Abstract

Serhiy V. Popov
ORCID: 0000-0002-1789-1474
Oleksandr I. Smiyan
ORCID: 0000-0001-8225-0975
Olena H. Vasylieva
ORCID: 0000-0003-4470-8740
Liudmyla A. Iusiuk[1]
Anastasiia O. Profatylo
ORCID 0000-0002-8032-7323
Tetyana V. Romanenko
Dmitro A. Govorun
Department of Pediatrics, Sumy State University, Sumy, Ukraine; [1]Neonatal Intensive Care Unit, Municipal Non-Profit Institution of Sumy Regional Council "Regional Clinical Children's Hospital", Sumy, Ukraine

ANTIBIOTIC-ASSOCIATED BLOOD CHANGES IN NEWBORNS

Objective. The objective of the study was to determine the chances of a decrease in CBC cells when using antibiotics in newborns.

Materials and methods. A total of 46 newborn infants who were hospitalized with the main diagnosis of hypoxic ischemic encephalopathy were examined. By gestational age, they belonged to the late-preterm and term groups. The newborns were divided into 2 subgroups. Group 1 – main group: 25 children who received antibiotics; group 2 – control group: 21 children who did not receive antibiotics. Group 1 was divided into 2 subgroups: Group 1a, 16 newborns who received 1 antibiotic and Group 1b, 9 newborns who received 2 antibiotics. Antibiotics were administered at age-related doses, intravenously, including semi-synthetic penicillins, cephalosporins, aminoglycosides, carbapenems, glycopeptides. The features of the analysis of blood (CBC) were studied.

Results. It was noted that in terms of general characteristics, the newborns of the main and control groups were comparable. When comparing the mean values of blood counts, a significant decrease in erythrocytes, leukocytes and erythrocytes was revealed in the group of newborns who received antibiotics in comparison with the control group. The absolute number of neutrophils was significantly lower in the group of newborns who received 2 antibiotics vs. the control group. The odds ratio calculation showed an increased risk of a decrease in cell levels with antibiotic therapy prescribed. Leukocytes were found to have the greatest chances of decreasing from the normative level – by 5.34 times, as well as erythrocytes – by 3.56 times. The absolute number of neutrophils decreased with the greatest chances when 2 antibiotics were administered – by 22 times.

Conclusions. In general, the antibiotic therapy leads to a decrease in the number of erythrocytes, leukocytes, platelets. This was most noted for leukocytes and erythrocytes. The absolute neutrophil count decreased most significantly with 2 antibiotics used.

Keywords: newborns, antibiotic therapy, complete blood count, cytopenia.

Corresponding author:
Serhiy V. Popov, Department of Pediatrics, Sumy State University, Sumy, Ukraine
e-mail: s.popov@med.sumdu.edu.ua

Резюме

Сергій В. Попов
ORCID: 0000-0002-1789-1474
Олександр І. Сміян
ORCID: 0000-0001-8225-0975
Олена Г. Васильєва
ORCID: 0000-0003-4470-8740
Людмила А. Юсюк [1]
ORCID: 0000-0002-8032-7323
Анастасія О. Профатило
ORCID 0000-0002-8032-7323
Тетяна В. Романенко
Дмитро А. Говорун

*кафедра педіатрії, Сумський
державний університет, м. Су-
ми, Україна;*
[1]*відділення інтенсивної терапії
новонароджених дітей, КНП
«СОР ОДКЛ», м. Суми, Україна*

АНТИБІОТИК-АСОЦІЙОВАНІ ЗМІНИ КРОВІ У НОВОНАРОДЖЕНИХ

Мета. Метою дослідження було визначення шансів зниження клітин загального аналізу крові під час використання антибіотиків у новонароджених.

Матеріали та методи. Усього було досліджено 46 новонароджених дітей, які перебували на стаціонарному лікуванні з основним діагнозом гіпоксично-ішемічна енцефалопатія. За гестаційним віком вони належали до груп пізньонедоношених і доношених. Новонароджені були поділені на 2 підгрупи. Група 1, основна, 25 дітей, які отримували антибіотики, група 2, контрольна група, 21 дитина, які не отримували антибіотики. У свою чергу, група 1 була розділена на дві підгрупи: група 1a, 16 новонароджених, які отримували 1 антибіотик та група 1b, 9 новонароджених, які отримували 2 антибіотики. Антибіотики вводилися у вікових дозах, внутрішньовенно, до них входили полісинтетичні пеніциліни, цефалоспорини, аміногликозиди, карбапенеми, глікопептиди. Вивчались особливості аналізу крові за основними показниками.

Результати. Зазначено, що за загальними характеристиками новонароджені основної і контрольної груп були порівняні. При аналізі середніх значень показників крові було виявлено достовірне зниження еритроцитів, лейкоцитів та еритроцитів у групі новонароджених, які отримували антибіотики, порівняно з контрольною групою. Абсолютна кількість нейтрофілів була достовірно низькою для групи новонароджених, які отримували 2 антибіотики, відносно контрольної групи. Розрахунок відношення шансів показав наявність підвищених шансів зниження кількості клітин крові при призначенні антибактеріальної терапії. Найбільші шанси зниження рівня від нормативного виявлено для лейкоцитів – в 5,34 рази, еритроцитів – в 3,56 рази. Абсолютне число нейтрофілів знижувалося з найбільшими шансами при введенні 2 антибіотиків – в 22 рази.

Висновок. Призначення антибактеріальної терапії призводить до зниження кількості еритроцитів, лейкоцитів, тромбоцитів. В найбільшої мірі це відзначалося для лейкоцитів та еритроцитів. Абсолютна кількість нейтрофілів найбільше значно знижувалася при використанні 2 антибіотиків.

Ключові слова: новонароджені, антибіотикотерапія, загальний аналіз крові, цитопенія.

Автор, відповідальний за листування:
Сергій В. Попов, кафедра педіатрії, Сумський державний університет, м. Суми, Україна
e-mail: s.popov@med.sumdu.edu.ua

Introduction/Вступ

The neonatal period is accompanied by a significant level of morbidity and mortality. Modern technologies for nursing and treating pathological conditions of newborns have led to an improvement in their survival rates. In no small part, this is due to the use of aggressive and invasive methods of diagnosis and treatment, which can increase the risk of infection. Along with a significant proportion of infectious diseases in the neonatal period, this leads to the widespread use of

antibacterial agents [1, 2]. Antibiotics are a key factor in the treatment of infectious diseases and significantly improve newborn survival. However, they also have a fairly wide range of complications. In addition to the formation of a pool of microorganisms with increased resistance, these include the development of microbiome disorders of varying degrees, antibiotic associated diarrhea, and allergic reactions [3, 4]. A number of authors note a decrease in the number of blood corpuscles. The mechanism of development of cytopenia is different and includes direct toxic effects on the bone marrow and/or myeloid precursors, antibody-mediated destruction of blood cells. Studies have established the dose-dependent effect of beta-lactam antibiotics on granulopoiesis [2, 5, 6, 7, 8]. Other authors reported about antibodies-mediated hemolytic anemia and thrombocytopenia. The degree of change in the number of blood cells can be significant and life-threatening [9, 10, 11]. At the same time, there is no uniform idea about the predominant damage to blood cells. Some authors point to predominantly detectable neutropenia, anemia and thrombocytopenia [12]. Others describe the development of thrombocytopenia when using antibiotics among the 4 main groups of drugs [10].

Objective

The objective of the study was to determine the chances of a decrease in CBC cells when using antibiotics in newborns.

Materials and methods

A total of 46 newborn infants who were hospitalized with the main diagnosis of hypoxic ischemic encephalopathy were examined. By gestational age, they belonged to the late-preterm and term groups. The newborns were divided into 2 subgroups. Group 1 – main group: 25 children who received antibiotics; group 2 – control group: 21 children who did not receive antibiotics. In turn, Group 1 was divided into 2 subgroups: Group 1a, 16 newborns who received 1 antibiotic and Group 1b, 9 newborns who received 2 antibiotics. Antibiotics were administered at age-related doses, intravenously, including semi-synthetic penicillins, cephalosporins, aminoglycosides, carbapenems, glycopeptides. The features of the analysis of blood (CBC) were studied according to the indicators of RBC – red blood cells; MCHC – mean corpuscular hemoglobin concentration; MCV – mean corpuscular volume; WBC – white blood cells; ANC – absolute neutrophils count; PLT – platelets;

MPV – mean platelets volume. The presence of differences between Group 1 and Group 2, as well as Group 1a and Group 1b with Group 2, was assessed. To assess the chances of developing cytopenia, reference values of the lower limit of normal and average values for RBC, WBC, ANC, PLT indicators were used [13, 14].

All statistical data were processed using a standard statistical formula. Continuous variables were confirmed for normal distribution by the Kolmogorov–Smirnov test and expressed as mean values ± standard error (M ± SE). Differences between the two groups in continuous variables were analyzed using an independent t-test for normal distribution. The odds ratio (OR) was obtained. For statistical significance calculating the criteria χ^2, Fisher (F), Student test (t) were used. P-value of < 0.05 was considered statistically significant.

All research methods and experiments have been examined and approved by the appropriate Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Results

General characteristics of the studied groups of newborns are presented in Table 1. The average body weight at birth was the smallest in Group 1b – 2638.85 ± 112.33 grams, the highest in Group 2 – 2865.25 ± 83.17 grams. At the same time, there was no significant difference between them. The average body length at birth was also the lowest in Group 1b children – 46.97 ± 0.61 cm and the highest for Group 2 – 47.72 ± 0.45 cm. This indicator also did not have significant differences between the study groups. The gestational age of newborns was within the values for the characteristics of late-preterm and term groups. This applied to children of all studied groups, no significant differences were found in this indicator, the mean values ranged from 35.21 ± 0.32 to 36.22 ± 0.23 weeks. The Apgar scores characterized the presence of asphyxia in children of all studied groups. The mean values of the assessment at the 1st minute of life were in the range from 3.9 ± 0.47 to 4.7 ± 0.54 units, there was no significant difference between the groups, and corresponded to the presence of moderate and severe asphyxia. There was a positive dynamics of assessment on the Apgar scale by the 5th minute of life. Its mean value ranged from 6.64 ± 0.59 units in Group 1a to

Table 1 – The general indexes of the newborns

Indexes	Group 1a (16)	Group 1b (9)	Group 1 (25)	Group 2 (21)
Birthweight, grams, mean ± SE	2723,11 ± 104,67	2638,85 ± 112,33	2698,35 ± 78,24	2865,25 ± 83,17
Length at birth, cm, mean ± SE	47,88 ± 0,41	46,97 ± 0.61	47.12 ± 0.37	47,72 ± 0.45
Gestation age, mean ± SE	35,21 ± 0,32	36,08 ± 0,44	36,16 ± 0,57	36,22 ± 0,23
Child's age of antibiotic therapy onset, days, mean ± SE	2,31 ± 0,41	1,87 ± 0,45	2,03 ± 0,31	2,34 ± 0,36
Child's age of analysis, days, mean ± SE	10,26 ± 0,48	9,97 ± 0,64	10,23 ± 0,38	9,76 ± 0,6
Apgar 1, mean ± SE	4,7 ± 0.54	3,9 ± 0,47	4,32 ± 0,39	4,6 ± 0,41
Apgar 2, mean ± SE	6,64 ± 0,59	6,96 ± 0,77	6,81 ± 0,46	7,01 ± 0,54
Boys, absolute value/%	9/56,25	5/55,56	14/56	12/57,14
Girls, absolute value/%	7/43,75	4/44,44	11/44	9/42,86
Mother's age, years, mean ± SE	26,82 ± 2,17	29,57 ± 2,2	27,81 ± 1,61	28,62 ± 1,7

Note: * - significant difference between indexes of Group 1a, Group 1b, Group 1 with Group 2

7.01 ± 0.54 units in Group 2. No significant differences were found between the study groups. The number of boys outnumbered girls and ranged from 55.56% to 57.14% in Group 1b and Group 2, respectively. The values did not differ significantly between all the study groups. The age of the mother of the children of the study groups was from 26.82 ± 2,17 to 29.57 ± 2.2 years in Group 1a and Group 1b, respectively. The mean values did not differ for the children of the study groups (p > 0.05). The start of antibiotic therapy was started in the early neonatal period and ranged from 1.87 ±

0.45 to 2.34 ± 0.36 days of life. No difference was found between groups (p > 0.05). The age of children when CBC was taken was at the beginning of the second week of life. It ranged from 9.97 ± 0.64 to 10.26 ± 0.48 days in Group 1b and Group 1a, respectively. The values did not differ significantly between all the studied contingents. Thus, the values of the general characteristics of the studied groups were comparable.

The results of the blood test parameters in the groups are presented in Table 2. The RBC value

Table 2 – The CBC indexes in newborn of studied groups (Main value and its error)

Indexes	Group 1a	Group 1b	Group 1	Group 2
RBC, 10^{12}/l	3.84 ± 0.14	3.62 ± 0.19	3.64 ± 0.12	4.1 ± 0.14
P with Group 2			0.016	
MCHC, g/l	349.37 ± 9.06	331.84 ± 11.22	343.59 ± 7.13	356.25 ± 11.87
P with Group 2				
MCV, fl	91.26 ± 3.93	89.21 ± 5.38	90.55 ± 3.12	91.44 ± 4.6
P with Group 2				
WBC, 10^9/l	6.13 ± 0.43	5.81 ± 0.53	5.92 ± 0.33	7.3 ± 0.46
P with Group 2		0.043	0.019	
ANC, units	6793.94 ± 167.55	6366.28 ± 178.23	6579.21 ± 130.19	7032.84 ± 163.54
P with Group 2		0.01	0.035	
PLT, 10^9/l	206.27 ± 19.21	220.36 ± 23.44	213.12 ± 14.68	274.68 ± 18.12
P with Group 2	0.014		0.011	
MPV, fl	8.34 ± 0.22	8.2 ± 0.32	8.43 ± 0.18	8.62 ± 0.21
P with Group 2				

Note: RBC – red blood cells; MCHC – mean corpuscular hemoglobin concentration; MCV – mean corpuscular volume; WBC – white blood cells; ANC – absolute neutrophils count; PLT – platelets; MPV – mean platelets volume

was lower in the newborns who received antibiotics than in the children who did not receive them. At the same time, a significantly lower value was found for Group 1 in comparison with Group 2 (p = 0.016). The MCHC parameter reflected the saturation of erythrocytes with hemoglobin. Its value tended to decrease in Group 1b children, but not significant. A similar picture was observed for the mean erythrocyte volume, MCV. The MCV value was smaller for the antibiotic-treated groups of children, but not significant. Analysis of the total number of leukocytes showed their lower value in Group 1a, Group 1b, Group 1 in comparison with Group 2. However, only for the pairs of Group 1b and Group 2, Group 1 and Group 2 the differences were significant (p = 0.043 and p = 0.019 respectively). The magnitude of the absolute number of neutrophils had a similar trend. It was smaller in children who received antibiotics. This confirmed a significantly lower ANC value but already in Group 1b children – 6366,28 ± 178,23 units in comparison with Group 2 – 7032.84 ± 163.54 units (p = 0.01) and in Group 1 – 6579,21 ± 130,19 units in comparison with Group 2 (p = 0.035). Platelet counts also decreased in children receiving antibiotic therapy. The PLT value was significantly lower in the newborns of Group 1a – 206.27 ± 19.21 10^9/l and Group 1 213,12 ± 14,68 10^9/l in comparison with the indexes Group 2 – 274.68 ± 18.12 10^9/l (p = 0.014 and p = 0.011 respectively). The average platelet volume did not show significant differences in the study groups. There was a tendency to its lower values in children treated with antibiotics, but not significant (p > 0.05).

Thus, the analysis of blood parameters showed a decrease in erythrocytes, leukocytes and platelets in children in the groups that received antibiotic therapy. In the case of the parameter of the white blood cells and absolute number of neutrophils, a significant decrease was observed for children who received 2 antibacterial drugs first of all.

To determine the magnitude of the chances of developing a decrease in the number of blood cells during antibiotic therapy (AB), the odds ratio was calculated (Figure 1). For erythrocytes, the reference value of the lower limit of the norm for the corresponding age and gestational age was used [13, 14]. The OR value was 3.56 units with a p value of 0.003. This indicated a 3.5-fold increase in the chances of erythropenia with antibiotics used. The calculation of the odds ratio for the likelihood of leukopenia was carried out in a similar way. The reference value of the lower limit of the norm was taken for age and gestational age. In this case, the OR value was 5.34 units with a p value of 0.03. Thus, leukopenia developed 5.34 times more often with antibiotic therapy than without it. A preliminary analysis showed that the absolute number of neutrophils for the general group of children in the main group will not show neutropenia at the lower limit of the norm. Therefore, the average value of the norm for age and gestational age was taken. In this case, the odds ratio was 3.81 units, but it was not reliable (p = 0.19). However, when taking the results of the ANC study in children who received 2 antibiotics,

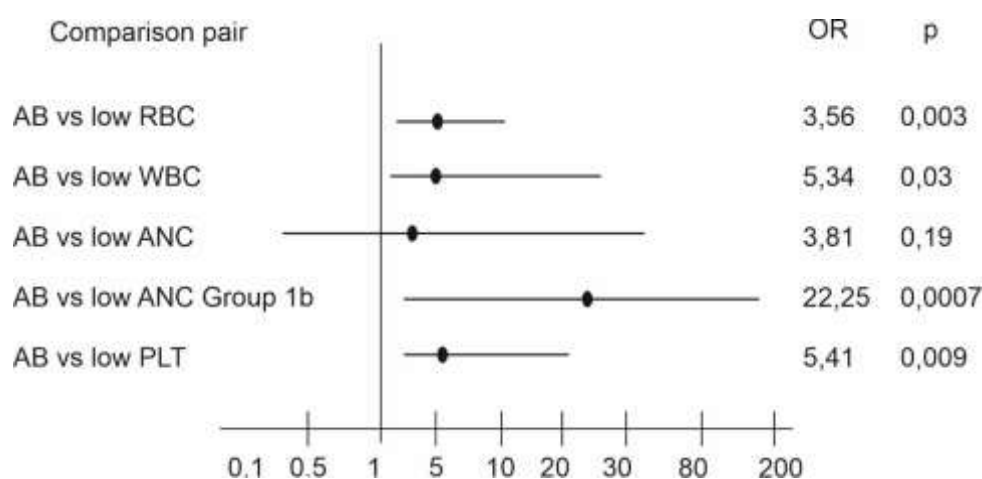| Comparison pair	OR	p
AB vs low RBC	3,56	0,003
AB vs low WBC	5,34	0,03
AB vs low ANC	3,81	0,19
AB vs low ANC Group 1b	22,25	0,0007
AB vs low PLT	5,41	0,009

Figure 1 – Dependence of the CBC changes and antibiotics use

the OR value was higher. The OR was 22.25 units with a p value of 0.0007. Thus, a decrease in the level of neutrophils occurred, but largely depended on the use of 2 antibiotics. The level of platelets in the main group decreased, however, just as for the ANC, the number of cases of decrease below the 5th percentile of the reference value was low. The mean platelet count was also taken for age and gestational age. In this case, the value of the odds ratio was 5.41 units with a value of p = 0.009.

Discussion

Adverse drug events (ADEs) have been known since the early days of medication. ADEs can damage many organs and systems, including the blood system, with development of the pancytopenia. Drugs that can lead to blood ADEs can be cytostatics, antiepileptics, antidepressants, and antibiotics [2, 5, 15]. It is indicated that adverse drug events can be detected in 19–51% of children who received intravenous antibiotics [6, 7, 8]. The most significant of these may be neutropenia, which is more often observed with intravenous administration. Anemia was 2–3 times less common, and thrombocytopenia was even less common [12]. Other authors indicate the development of hemolytic anemia and thrombocytopenia in patients receiving carbopenems [15, 16]. Other works describe a high frequency of agranulocytosis, which with a

frequency of 12% can be caused by beta-lactam antibiotics [9]. According to other researchers, thrombocytopenia is an important component of adverse drug events and antibiotics are responsible for the implementation of at least 2 mechanisms of antibody formation with the development of drug-induced immune thrombocytopenia [10, 11]. In our study, the odds ratio of 3.56 and 5.34 units were identified for the development of eritocytopenia and leukocytopenia respectively, which, to a certain extent, corresponds to the available literature data. However, this cannot be said about the level of granulocytes. According to our analysis, the decrease in the absolute number occurred with an increase in chances of 3.81, depending on the appointment of antibiotic therapy, but not significantly. However, when calculating the odds ratio in the group of newborns who received 2 antibiotics, OR was the highest – prescribing AB in 22 times increased the chances of a decrease in the absolute number of neutrophils. The degree of platelet reduction, according to our data, was still less than the rest of the studied blood cells. Perhaps this depended on the characteristics of the identified groups of newborns or/and the characteristics of the laboratory complex. The degree of platelet reduction was less, but relative to the average value, the chances of a decrease in their level with antibiotic therapy increased 5.41 times.

In general, antibiotic therapy leads to a decrease in the number of erythrocytes, leukocytes, platelets.

Leukocytes were found to have the greatest chances of decreasing from the normative level –

by 5.34 times, as well as erythrocytes – by 3.56 times. The absolute number of neutrophils decreased with the greatest chances when 2 antibiotics were administered – by 22 times.

Prospects for further research suggest conducting a study on a large sample of patients.

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Conflict of interest/Конфлікт інтересів

The authors declare no conflict of interest.

Information about the authors/Відомості про авторів

Сергій Віталійович Попов, ORCID: 0000-0002-1789-1474; Сумський державний університет, професор кафедри педіатрії, Суми, Україна.

Олександр Іванович Сміян, ORCID: 0000-0001-8225-0975; Сумський державний університет, завідувач кафедри педіатрії, Суми, Україна.

Олена Геннадіївна Васильєва, ORCID: 0000-0003-4470-8740, Сумський державний університет, асистент кафедри педіатрії, Суми, Україна.

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Анастасія Олександрівна Профатило, ORCID 0000-0002-8032-7323, Сумський державний університет, аспірант кафедри педіатрії, Суми, Україна.

Тетяна Володимирівна Романенко, Сумський державний університет, лікар-інтерн, Суми, Україна.

Дмитро Андрійович Говорун, Сумський державний університет, студент, Суми, Україна.