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Immunoflazid® in the prevention of infectious disease in infants
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The aim of this work was to evaluate the efficacy and safety of Immunoflazid® for the prevention of infectious diseases in children in the first year of life.

Methods. A comparative controlled study in parallel groups of healthy newborns. According to the results of randomization, patients were divided into 2 groups. The study group included 39 children who are over 14 days of receiving Immunoflazid® per day. The control group consisted of 36 infants who did not receive the drug. The effectiveness of preventive measures was assessed by the absence of disease over a period of six months follow-up.

Results. Studies have shown that children of the main group in the 4-fold decreased the incidence of infectious diseases, the relative risk of disease decreased by 75%, the chances of the disease decreased to 0.03. During the administration of the drug is not registered a single case of side effects.

Conclusions. Immunoflazid® — an effective and safe means of preventing infectious diseases in children in the first year of life.

Key words: Immunoflazid®, the children of the first year of life, prevention of infectious diseases.

Introduction

Epidemiological studies conducted in several European countries indicate that on average, each child experiences from 3 to 6 episodes of acute respiratory viral infection (ARVI) during the year [7,8,13]. The high incidence of acute respiratory viral infection is explained by the ease of infestation and the high antigenic variability of viruses, their ability to persist in the child's body against the background of an immature immune system, and the presence of a large number of serotypes of bacterial pathogens. The viral infections predominate among diseases of the respiratory tract in children. The total number of viruses that cause acute respiratory viral infection is more than 200. Mixed viral and viral-bacterial infections of the respiratory tract are of great importance [1, 4, 9].

In addition to the direct etiologic causes of acute respiratory viral infection, several factors should be noted that contribute to the development of repeated episodes of respiratory infection in children, including an adverse premorbid background, perinatal involvement of the central nervous system, intrauterine infection, immaturity, prematurity, etc., which adversely affect the condition of all systems of the developing body and, in particular, complete development of immunity [1, 7, 8].

Of a great importance in the susceptibility of children to ARVI are the physiological (critical) periods of the development of the immune system of the child, which largely determine the course and outcome of diseases in childhood. The first critical period falls on the age of up to 28 days of life, the second - up to 4-6 months, the third - up to 2 years, the fourth - up to 4-6 years, the fifth - up to 12-15 years. In this case, the child is the least protected during the first two critical periods. This is due to the fact that during the first critical period (neonatal period) the immunity of the child is passive, as it is provided exclusively by maternal antibodies, while the own immune system is in a state of suppression. Characteristic for this period is the propensity to generalize the process, to septic states, high sensitivity to viral infections. During the second critical period (4-6 months), maternal antibodies are destroyed, and the developing primary immune response is provided through the synthesis of IgM and does not leave immunological memory [11]. In this case, the

insufficiency of the local immunity system is manifested by repeated ARVI, intestinal infections, skin diseases. Thus, the age of 0-6 months is characterized by increased sensitivity of the child to ARVI and is a feature of its ontogeny. And in the presence of a protracted and complicated course of acute respiratory viral infection, the immune system and, consequently, the mechanisms of anti-infective protection are inadequate when “the viruses pass sentence and the bacteria carry it out” [2, 11].

The continuing tendency of complications to increase caused by infections, especially in the first half of the child's life, necessitates the search for effective and safe methods of their treatment and prevention aimed at preventing and correcting deviations in the health status of children [1, 7, 9]. When choosing the tactics of ARVI therapy in infants, special attention is paid to the safety of medicines, their pharmacodynamic capabilities to suppress the activity of the viral infection and to increase the nonspecific immunological defense of the organism, both locally and at the system level [4, 8, 13].

For a long period of time the antiviral, antioxidant and immunomodulating properties of flavonoids were under study worldwide. Flavonoids are the group of natural biologically active compounds – benzopyrone derivatives. Based on the results of experimental studies and clinical trials, the effectiveness of flavonoids in the prevention of respiratory, immune, oncological, neurodegenerative, cardiovascular and other diseases has been demonstrated. Given this, one of the promising areas in the treatment of ARVI in children is the use of drugs from the group of bioflavonoids. So, in the last 10 years the effectiveness and safety of the domestic antiviral drug from the group of bioflavonoids – Immunoflazid®, syrup (“SMC “Ecopharm”, Ltd. (Ukraine)) has been actively studied. 100 ml of the syrup contains 2 ml of the liquid extract of Proteflazid, obtained from a mixture (1:1) of herbs: tufted hair grass (*Herba deschampsia caespitosa* L.) and bush grass (*Herba Calamagrostis epigeios* L.); 1 ml of the extract contains at least 0.32 mg/ml of flavonoids in terms of rutin. Flavonoids, which are part of Immunoflazid® syrup, belong to the groups of flavone and flavonol glycosides. It has been proved that the flavonoids as active substances of Immunoflazid®, suppress the replication of DNA and RNA of respiratory viruses, incl. influenza, both in vitro and in vivo. The mechanism of antiviral action of the drug includes the inhibition of virus-specific enzymes of DNA polymerase, thymidine kinase and reverse transcriptase; anti-influenza effect – suppression of neuraminidase activity, inhibition of RNA synthesis of viruses and induction of synthesis of endogenous α - and γ -interferons. Through strengthening the processes of apoptosis the drug contributes to a faster elimination of virus-infected cells and the prevention of chronic diseases against the background of latent viral infections. The results of clinical studies have shown that under conditions of prolonged daily use of Immunoflazid® syrup there is no inhibition of the activity of IFN- α and IFN- γ formation, which normalizes the patient's immune status [5, 10, 12, 15]. Immunoflazid® protects the mucous membranes of the upper respiratory tract, normalizing the indices of local immunity (lactoferrin, sIgA and lysozyme); strengthens the antioxidant status of cells by inhibiting free radical processes, which prevents the accumulation of lipid peroxidation products, reduces intoxication, promotes recovery of the body after the infection and adaptation to unfavorable environmental factors [10, 14].

Clinical studies on the use of Immunoflazid® in various infectious diseases have demonstrated its high clinical and immunological efficacy and the absence of side effects. Immunoflazid®, having a high safety profile, is approved for use in children from birth [8, 10, 14].

The purpose of the study was to evaluate the efficacy and safety of Immunoflazid® syrup, which is used to prevent infectious diseases in children of the first year of life.

Material and methods

A comparative controlled study was carried out in parallel groups among healthy children of the Neonatal Department of Maternity Hospital No. 7 in Odessa, born from mothers with TORCH infections. Relatives of all patients received oral information about all the procedures of the study and provided their informed consent to participate in the study. According to the results of randomization, patients were divided into two groups. The main group, 39 children, received

Immunoflazid® 0.25 ml (1/2 treatment dose) twice a day for 14 days after birth, according to the package insert. The control group consisted of 36 newborns who did not receive the drug.

All children after discharge from the hospital were observed in outpatient settings for six months, the disease was recorded in the medical records. The effectiveness of preventive measures was assessed by the absence of morbidity for the entire observation period.

There were no statistically significant clinical differences between the groups. The average age of the mothers in the main group was 26.57 ± 1.32 , in the control group - 25.73 ± 1.41 years. All the children of the main group were mature; the average gestational period was 38.44 ± 0.59 weeks. The average weight of newborns was 3101.81 ± 166 g, body length - 49.18 ± 1.09 cm, head circumference - 33.15 ± 0.87 cm, chest - 32.81 ± 0.73 centimeters. The average Apgar scores for the first minute of life were 7.81 ± 0.15 points, on the fifth - 8.31 ± 0.23 .

All children of the control group were also mature; the average gestational period was 39.05 ± 0.39 weeks. The average weight of newborns was 3263.82 ± 154.50 g, body length - 49.87 ± 0.69 cm, head circumference - 33.38 ± 0.76 cm, chest - $33,1 \pm 0.59$ centimeters. Apgar scores for the first minute of life were 7.64 ± 0.18 , the fifth - 8.50 ± 0.18 points.

The statistical analysis of the obtained data was carried out using Statistica 8.0, MedCalc 14.8.1 and Microsoft EXCEL 2010 packages with the integration of the AtteStat 12.5 add-on, the Internet calculator SISA (Simple Interactive Statistical Analysis). The average sample values of quantitative characteristics are given in the text in the form $M \pm m$, where M is the mean sample, and m is the error of the mean. The shares (percentages) are presented with 95% confidence intervals. In all statistical analysis procedures, when testing null hypotheses, the critical significance level p was assumed to be 0.05. Study of the relationship between pairs of discrete qualitative characteristics was carried out using the analysis of paired contingency tables, where the values of Pearson's statistics were estimated as X-square (X^2), achieved significance level (p), odds ratio (OR), relative risk reduction (RRR) and number of patients who required treatment for a certain time to achieve a positive result in one patient (PR), with the definition of 95% confidence intervals. To estimate the relation strength between qualitative characteristics, the Cramer coefficient was used, ϕ [3, 6].

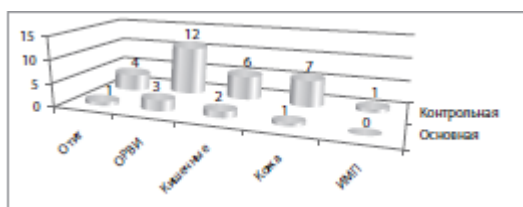


Fig. 1. Distribution of infections depending on the site of localization

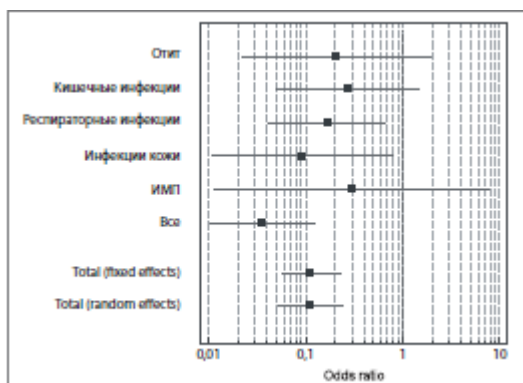


Fig.2. Efficacy of preventing infectious diseases in children who received Immunoflazid® syrup

Evaluation of the efficacy of preventing infectious diseases in infants who received Immunoflazid®

Localization of infection	RRR % (95% CI)	OR (95% CI)	PR (95% CI)	P
Otitis, moderate	77 (-108-99)	0,21 (0,01-2,18)	11 (7—o)	0,14
Diseases of the upper respiratory tract	77 (21-94)	0,16 (0,03-0,73)	4 (3-20)	0,006
Intestinal infections	69 (-57-95)	0,27 (0,03-1,65)	9 (5—<>)	0,1
Skin Infections	88(17-99)	0,09 (0,01-0,8)	5 (4-44)	0,009
Urinary tract infection	100 (-14,93-100)	0,00 (0,00-16,3)	36 (36-<<)	0,29
All registered infections	79 (61-88)	0,03(0,01-0,14)	2(1-2)	0,0001

Results and discussion

The examined main group included 21 (53.84%, 95% confidence intervals (CI) 38.35-69.64) boys and 18 (46.14%, 95% CI 30.35-61.64) girls. In the control group there were 17 (47.22%, 95% CI 30.69-63.3) boys and 19 (52.78%, 95% CI 36.69-69.3) girls.

A retrospective analysis of the health status of the children for a six month-period of life showed that only 7 subjects fell ill in the main group (17.94%, 95% CI 5.94-30.05). One of them was diagnosed with acute otitis (2.56%, 95% CI -2.57-8.57) and streptoderma (2.56%, 95% CI -2.57-8.57), two children – with intestinal infection (5.12%, 95% CI -1.75-13.75), three – with ARVI (7.69%, 95% CI -0.86-16.86).

In the control group, the morbidity was 4.3 times higher within the same period - 30 children (83.33%, 95% CI 70.72-95.27) became ill. According to the nosofoms, the patients were distributed as follows: acute middle catarrhal otitis - 4 children (11.11%, 95% CI 0.77-21.22), intestinal infections caused by opportunistic microflora (*Proteus mirabilis*, *Campilobacter coli*, *Enterobacter cloacae*, *Enterobacter aerogenos*) – 6 children (16.67%, 95% CI 4.72-29.27), acute respiratory viral infection - 12 (33.33%, 95% CI 17.64-48.36), skin infections - 7 (19.44%, 95% CI 5.4-32.6), urinary tract infections - 1 child (2.77%, 95% CI -2.59-8.13). The data in the graphical presentation is shown in Figure 1.

When comparing the incidence in the study groups, a statistically significant reduction was observed in the incidence rate in the main group of children receiving Immunoflazid®: $X^2 = 32.12$, RRR-79% (95% CI 61-88%), OSH-0.03 (95% CI 0.01-0.14), PR - 2 (95% CI 1-2), Cramer coefficient, $\phi = -0.68$, $p = 0.0001$. Immunoflazid® proved to be a highly effective agent for the prevention of the incidence of respiratory infections: $X^2 = 7.63$, RRR-77 (95% CI 21-94), OR - 0.16 (95% CI 0.03-0.73), PR-4 (95% CI 3 -20), Cramer coefficient $\phi = -0.32$, $p = 0.006$. Also, statistically significant differences in the groups were observed in skin infections: $X^2 = 6, 85$, COP-88 (95% CI 17-99), RRR-0.09 (95% CI 0.01-0.8), PR - 5 (95% CI 4-44), Cramer coefficient $\phi = -0.3$, $p = 0.009$.

When assessing the quality of prevention of other types of infections, the effectiveness of the drug was lower. For intestinal infections ($X^2 = 2.6$, RRR-69 (95% CI -67-95), OR-0.27 (95% CI 0.03-1.65), PR-9 (95% CI 5 -00), Cramer coefficient $\phi = -0.18$, $p = 0.1$), in moderate otitis and urinary tract infections there were no statistically significant differences in the study groups of children. The comparison data in the groups are presented in the table and in Figure 2.

In the main group of observed children, all diseases (Figure 1) proceeded exclusively in mild form; the average duration of the disease was 6 ± 0.7 days. No side effects with the administration of Immunoflazid® syrup in children of the main group were observed. In the control group, 30% of children had a moderate period of infection. Severe forms are not noted. The average duration of the disease was 8.25 ± 0.45 days.

Conclusions

1. The study results demonstrate the high efficacy of Immunoflazid® (syrup) in the prevention of infectious diseases in children of the first year of life.

2. Immunoflazid® syrup is used to prevent infectious diseases in children from birth according to the scheme: 0.25 ml (1/2 treatment dose) twice a day (according to the package insert) with a course of 14 days. It reduces the incidence, duration, and severity of infectious diseases in children of the first year of life.
3. Immunoflazid® in clinical use is well tolerated by children and does not cause side effects, which is confirmed by its high safety profile.

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