

S.A Kramarev¹, O.I. Grynevych², O.B. Tonkovid³, O.V. Vyhovskaia¹ Meta-analysis of results of clinical studies on the efficacy of flavonoids in viral and viral-bacterial diseases in children

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Summary. The work shows a meta-analysis of clinical studies of flavonoids effect on the efficiency of reducing fever and intoxication syndrome during viral and viral-bacterial diseases in children. The meta-analysis involving 2,699 children, confirms the efficacy and safety of drugs that contain flavonoids: Proteflazidum, Immunoflazidum, Flavozidum (NPK "Ecopharm", Ukraine) and proves an anti-relapsing activity of these drugs.

Key words: Proteflazidum, Immunoflazidum, Flavozidum, meta-analysis, viral diseases, children, intoxication syndrome, fever.

Instruction

Viral-bacterial and viral diseases are the most widespread and most urgent pathology of childhood, which occupies a leading position in the structure of children's diseases. The diseases are characterized by multiple organ tropism causing a loss of almost all organs and systems of the child: respiratory, gastrointestinal, cardiovascular, nervous system and others. Thus, in children compared with adults, there is a more severe disease with frequent development of serious complications and chronicity of the pathology.

The treatment of viral and viral-bacterial diseases should be combined, etiopathogenetic, help prevent relapses and complications, to be effective, safe and tailored to suit the child's body.

The drugs that possess combined properties and both antiviral and immune corrective activity, proven efficacy and safety, include drugs that contain flavonoids of wild grass plants of tufted hair grass (*Herba Deschampsia caespitosa* L.) and bush grass (*Herba Calamagrostis epigeios* L.): Proteflazidum, Immunoflazidum, Flavozidum (NPK "Ecopharm", Kyiv, Ukraine).

Preclinical and clinical studies from various research institutes and clinics have proved the existence of a direct antiviral, immunotrophic, apoptosis modulating and antioxidant actions with drugs containing flavonoids. This pharmacodynamics of drugs determines the feasibility of their prescription for the treatment of acute, latent and chronic forms of viral and viral-bacterial infections.

Table 1

Identifier of Publications, Nosology, the Amount of the Children Included in the Meta-Analysis According to the Research

No.	Identifier	Nosology	Amount of Children
1	T.A. Kriuchko, 2002	Neurinfection	20
2	I.A. Shapovalova, 2003	Sore throat	220
3	T.A. Nikofova, 2004	Epstein-Barr virus infection	26
4	A.I. Hley, 2005	Infectious mononucleosis	27
5	Ye.V. Usachova, 2005	Infectious mononucleosis	38
6	Ye.Ye. Chernyshova, 2005	Herpes virus infection	199
7	S.V. Herasimov, 2006	Herpetic gingivostomatitis	38
8	T.A. Kriuchko, 2006	Herpes virus infection	62
9	S.V. Herasimov, 2007	Herpetic gingivostomatitis	36
10	Ye.I. Yulish, 2007	Recidivous obstructive bronchitis	105
11	Yu.P. Kharchenko, 2007	Infectious mononucleosis	60
12	S.A. Kramarev, 2007	Herpes virus infection	80
13	S.A. Kramarev, 2008	Epstein-Barr virus infection	35
14	T.A. Kriuchko, 2008	Herpes virus infection	58
15	S.A. Kramarev, 2008	Epstein-Barr virus infection	35
16	M.P. Prokhorova, 2008	ARVI	35
17	Ye.I. Yulish, 2008	Herpes virus infection	350
18	A.P. Volosovets, 2008	ARVI	35
19	Ye.I. Yulish, 2009	ARVI	80
20	P.I. Sichenko, 2009	ARVI	120
21	S.S. Turlibekov, 2011	Cytomegalovirus infection	48
22	F.M. Shamsiev, 2011	Acute pneumonia	169
23	Ye.I. Yulish, 2011	Herpes virus infection	130
24	S.A. Kramarev, 2011	Epstein-Barr virus infection	60
25	Ye.I. Yulish, 2011	Herpes virus infection	130
26	A.A. Zaliziuk, 2011	Community-acquired pneumonia	120
27	S.A. Kramarev, 2012	Herpes virus infection	80
28	N.I. Tokarchuk, 2012	ARVI and flue	50
29	Ye.I. Yulish, 2013	Herpes virus infection	140
30	S.A. Kramarev, 2014	Infectious mononucleosis	243
	Total		2,699

Objective: to verify the effectiveness of reducing flavonoids intoxication syndrome and fever in viral and bacterial diseases in children and the formation of the evidence base, to conduct a meta-analysis of clinical studies and long-term results of application of Proteflazidum, Immunoflazidum and Flavozidum on the following parameters: children without age restrictions, viral infections and viral and bacterial etiology, the presence of intoxication syndrome and fever.

Material and Methods

The meta-analysis included 30 clinical studies involving a total of 2,699 children aged 3 days to 18 years, from 2002 to 2014. Selected 30 publications of clinical results of cohort studies met the search criteria. In the primary selection, not all studies were consistent with the requirements of the classical meta-analysis due to the lack of a comparison group; the research was presented as cohort studies without comparison group. In this connection, to evaluate the effectiveness of drugs containing flavonoids, febrile children with intoxication syndrome and meta-analysis included only study with a comparison group. Based on the selected studies a publication identifier is drawn, which includes the main author, year of publication, nosology, the number of children taking flavonoids (table 1). Based on assessments of the effectiveness of the impact of flavonoids in the body temperature and intoxication syndrome in children with viral-bacterial and viral diseases obtained in separate studies we conducted a quantitative synthesis and evaluation of clinical effects in the form of meta-analysis to assess the statistical significance of the results. For the statistical analysis a licensed version of the Stat 12 statistical package was used.

Results and Discussion

To assess the normalization frequency of body temperature during the observation period five studies were selected that met the criteria for analysis. These studies included children with the following types of pathology: Epstein-Barr virus infection (EB infection), Infectious mononucleosis and Herpes virus infection. Given the different nosology and severity of the disease, an important aspect is the normalization of body temperature in the control points of observation. In the studies a gradual reduction of fever was reported without substantially changing the direction of speakers. Not all studies revealed statistically significant differences in the normalization of fever surveillance at checkpoints between the study and control group. The study of T.A. Nikiforova et al., 2004 shows a trend towards a higher frequency of normalization of temperature on the intake of flavonoids against the control group - the odds ratio OR=3,5 (95%CI: 0,7-17,8), p=0,126 [14]. In a study of S.A. Kramareva et al., conducted in 2012, with the herpes virus infection results in groups are comparable: OR=1 [10]. In a study of S.A. Kramareva et al., conducted in 2014, in infectious mononucleosis revealed

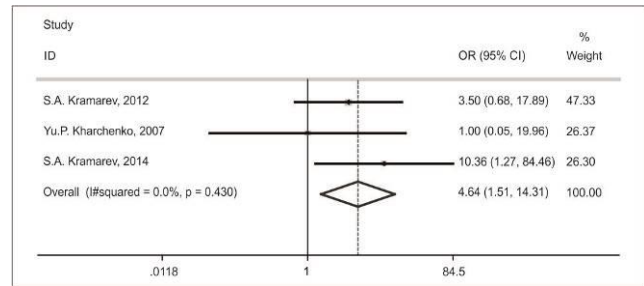


Fig. 1. Meta-analysis of the likelihood of removal the fever in stage of completion of the study or test points of observation (estimate odds ratios in children with viral diseases)

statistically significant differences and better results in the main group: OR=10,4 (95%CI: 1,2-84,4), p=0,012 [8]. Assessment of heterogeneity of a model: I²=0,0%, p=0,430, which indicates the homogeneity of the effect of increasing the frequency of removal of fever in different studies. Integral estimate of the odds ratio indicates a statistically significant increase in the probability of temperature normalization in children while taking drugs flavonoids in 4.64 times as compared with the control group of basic therapy: OR=4,64 (95% CI: 1,5-14,3). These heterogeneous results indicate the sensitivity of the normalization frequency of body temperature to the parameters of severity and nosology of the disease, but no dependence on the dosage and dosage form of the drug was revealed (fig. 1).

According to the results of expert assessment of the results of primary research on the criteria to identify the frequency of intoxication syndrome in the control observation points five studies were selected: two cohort and three comparative ones. The meta-analysis included only comparative studies that showed a significant increase in the probability of relief intoxication syndrome in children while taking study medications compared to the control group: S.A. Kramarev et al., 2012 — OR=9,0 (95%CI: 0,6-143,9), p>0,05 [10]; S.A. Kramarev et al., 2014 — OR=8,8 (95%CI: 1,9-40,8), p<0,01 [8]; Yu.P. Kharchenko et al., 2007 — OR=1,25 (95%CI: 0,1-22,9), p>0,05 [25]. Integral assessment indicates significant improvement (odds ratio OR = 6.6 (95% CI: 2,0-21,1), p <0.01) the effectiveness of therapy, which is manifested in arresting of intoxication syndrome in children when taking flavonoids. Assessment of heterogeneity of model: I²=0,0%, p=0,486, which indicates the homogeneity of the effects of increasing the frequency of intoxication syndrome elimination in different studies (fig. 2).

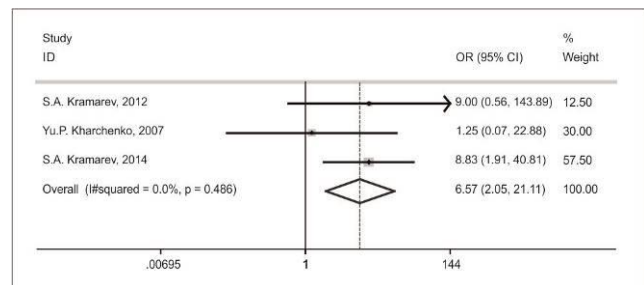


Fig. 2. Meta-analysis of the likelihood of removal of intoxication syndrome (estimated odds ratio OR) in children with viral diseases

The cohort clinical studies without comparison group confirm the effectiveness of flavonoids to eliminate intoxication syndrome in children: S.A. Kramarev et al., 2008 noted that the normalization of 14 days was recorded in 55.0% of patients with chronic EBV infection [11]; S.A. Kramarev et al., 2014 - normalization on day 14 was detected in 73.3% of patients with infectious mononucleosis. [8] T.A. Kriuchko et al., 2006 registered improvement in the general state of more than one third of patients by reducing symptoms of intoxication already on the fifth day of treatment with flavonoids [12]. P.I. Sichnenko et al., 2009 found on the background of the treatment with flavonoids a decrease of toxicity in 90% of children already on 2-3 days of the treatment [21]. In a study of A.A. Zaliziuk, 2011 [7] in the group of children treated with flavonoids, there has been a reduction of intoxication syndrome (6.67 + 0.32 days, compared to 10.7 ± 0.8 days in the control group, p < 0.05) (Fig. 2).

Information on the comparative analysis of the duration of fever and intoxication syndrome in children while taking study medication may be found much more frequently. Meta-analysis of the duration of fever included 10 studies on the following nosology: influenza, ARVI, sore throat, infectious mononucleosis, and cytomegalovirus and herpes virus infection. In all studies as described below reduction of the fever duration was mentioned in patients receiving drugs flavonoids as compared with the control group (standard therapy). Average time of the fever duration reduction was 3.1 days with considerable fluctuations on individual research: S.A. Kramarev et al., 2012 $r - \Delta = -1,4$ days [10], S.V. Herasimov et al., 2006 $-\Delta = -5$ days [6]; S.S. Turlibekov, 2011 $-\Delta = -2,5$ days [24]; S.V. Herasimov, 2007 $-\Delta = -2$ days [2]; Yu.P. Kharchenko et al., 2007 $-\Delta = -5$ days [25]; Ye.I. Yulish, 2008 $-\Delta = -1.29$ days [19]; Ye.I. Yulish et al., 2009 $-\Delta = -6.4$ days [15]; N.I. Tokarczuk et al., 2011 $-\Delta = -4.6$ days [23]; I.A. Shapovalova, 2002 $-\Delta = -1.3$ days [27]; S.A. Kramarev et al., 2014 $-\Delta = -1.4$ days [8]. Assessment of heterogeneity of a model: $I^2=93.5\%$, $p=0.0001$, suggesting heterogeneity of the effect of the fever duration reduction in different studies.

The effect size indicator was the basis of the analysis of changes in quantitative and comparative assessment. In literature, this figure is found under the name of "standardized mean difference" (SMD). The standardized mean difference is used as an effective statistics in the meta-analysis that evaluates the results of the study, but the measurements are presented in different units and have

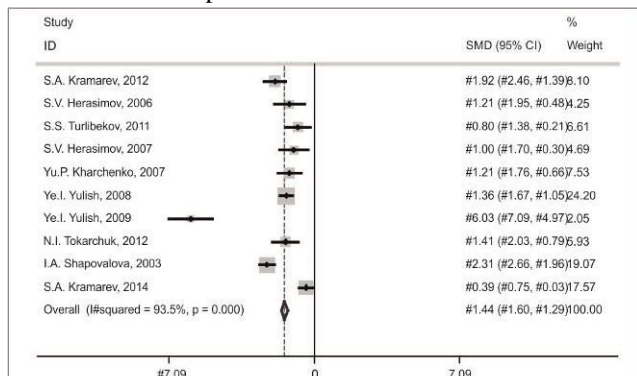


Fig.3. Meta-analysis of the duration of fever in children of the main ISSN 1992-5913 Modern Pediatrics 5(61)/2014

group (Proteflazidum, Immunoflazidum, Flavozidum) compared with the control group (standardized mean difference of children with viral and viral-bacterial diseases)

different dynamics and the absolute amount of variability indicators. In this case it is necessary to standardize the results of studies in a single scale, before they can be combined. Standardized mean difference reflects the magnitude of the effect resulting from intervention (dosing) for each study taking into account variability of results when compared with the control group, i.e. evaluation of a significant reduction in the duration of fever in the study group (fig. 3).

Integral size of the standardized difference in duration of fever is SMD=-1,4 (95%CI: -1,6 — -1,3), p<0,001. According to the Cochrane recommendations (Paul D Ellis / The Essential Guide to EFFECT SIZES, — UK, Cambridge, 2010. — P. 41), if the absolute value of the standardized difference (effect size) is greater than 0.8, we can speak of a pronounced effect - a significant excess of efficiency in the main group to reduce the duration of fever compared with the control group. Considerable heterogeneity results (coefficient heterogeneity $I^2 = 93,5\%$) may be due to various research parameters (severity of the pathological process, various diagnoses, etc. Fig. 3).

Besides the fever duration intoxication syndrome has an important clinical value. Under this option six cohort comparative clinical studies were selected, which included the following nosology: influenza, ARVI, community acquired pneumonia, infectious mononucleosis, and cytomegalovirus and herpes virus infection. Average time of intoxication syndrome duration reduction in comparison with the control group was 3.1 days with considerable fluctuations of individual research: the study of S.A. Kramareva et al., 2012 $-\Delta = -3,3$ days [10], E.I. Yulish et al., 2009 $-\Delta = -6,4$ days [15]. Assessment of heterogeneity of a model: $I^2=96.0\%$, $p=0.0001$, suggesting heterogeneity of the effect of reducing the duration of intoxication syndrome in different studies.

The standardized effect size reduction of the duration of intoxication syndrome in the study group on the background of the subjects of drugs SMD=- 1.84 (95%CI: -2.1 — 1,6), p=0.0001. According to all presented studies, the value of the more pronounced effect of reducing the duration of intoxication syndrome in the study group was statistically significant (p<0,05) (fig. 4).

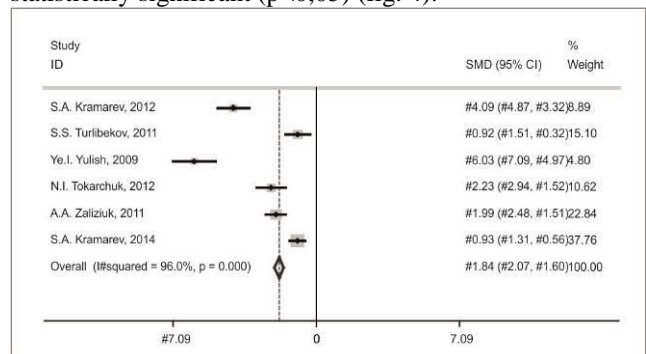


Fig. 4. Meta-analysis of the duration of intoxication syndrome in children of the main group (Proteflazidum, Immunoflazidum, Flavozidum) compared with the control group (standardized mean difference of children with viral and viral-bacterial diseases)

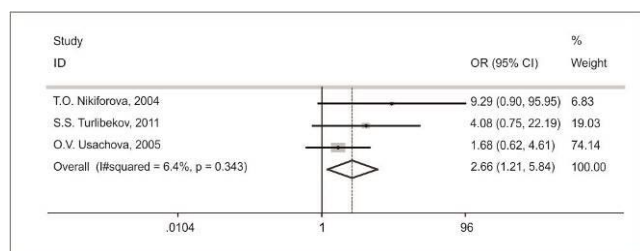


Fig. 5. A meta-analysis of frequency normalization of the number of leukocytes and lymphocytes (estimated odds ratio OR) in children with herpes virus infections

Laboratory criteria of fever and intoxication symptoms are a change in the blood count - leukocytosis and lymphopenia. Normalization of these indicators can serve as assessment of the effectiveness of the predominant flavonoids. A preliminary analysis revealed three studies that could be associated with the frequency of the normalization of leukocytes and lymphocytes in infectious mononucleosis (E.V. Usachova et al., 2005. [4]), cytomegalovirus infection (S.S. Turlibekov, 2011. [24]), and EBV infection (T.A. Nikiforov et al., 2004 [14]). At the end of the study the study group had a high level of normalization of these indicators: T.A. Nikiforov et al., 2004 - 92.9% of patients [14], S.S. Turlibekov, 2011 - 91.3% [24], E.V. Usachova et al., 2005 - 88.2% [4]. In the comparison group the restoration of the normal levels of white blood cells and lymphocytes was detected significantly less often (58.3%, 72.0%, 52.4%, respectively). Assessment of heterogeneity of a model: $I^2=6.40\%$, $p=0.343$, which indicates the homogeneity of the effects of increasing the normalization frequency of leukocytes and lymphocytes in different studies (fig. 5).

The results indicate a significant increase in the effectiveness of treatment when including flavonoids in the scheme of therapy that at the time of completion of the study is shown in increase of the normalization likelihood of leukocytes and lymphocytes in the main group by 2.7 times compared to the control group (odds ratio, $OR=2.66$ (95%CI: 1.2—5.8), $p=0.015$) (fig. 5).

When using the flavonoids in the therapy of viral and viral-bacterial diseases not only the immediate improvement of the clinical efficacy of treatment is of great importance. Actual aspects are the long-term outcomes and the frequency of relapses. To assess the frequency of relapses a long period of observation is required, which is more common in the cohort clinical studies without a comparison group. The analysis of long-term results generally confirms the prevalence of effective treatments to include flavonoids (Proteflazidum, Immunoflazidum, Flavozidum). In a study of A.I. Hley, 2005 ($n = 27$), there is no recurrence during follow-up for six months [3]. In a study of E.E. Chernysheva, 2005 ($n = 199$) arresting acute effects of infection was observed in 67% of children, relapsing course of chronic herpes virus infection was translated into a latent course in 64% of children [26]. All observed children showed decrease in 2.5 times of the amount and duration of recurrent respiratory diseases and their complications frequency [26]. E.I. Yulish et al., 2007 ($n = 199$) indicated that the use of drugs on the background of flavonoids in children with herpes infection symptoms of intoxication usually disappeared on the first and second day from the start of treatment [17]. In children with respiratory

mycoplasmosis and chlamydia the signs of intoxication disappeared mainly on the second day from the start of treatment, within six months there was no relapse of obstructive bronchitis in half of the children from the group with active infection course and in over 2/3 of the second group of patients with latent course. Flavonoids in the complex treatment of children helped eliminate acute signs of infection in 67% of children and transfer the disease from relapsing in latent course in 64% of patients [17]. T.A. Kriuchko et al., 2008 ($n = 58$) recommend the use of flavonoids as anti-relapsing treatment of herpes virus infections, observation results show that 17% of patients reported no recurrence of disease, 27.8% of patients had no recurrence during the first year, and 1-2 relapses occurred during the second year, 41.4% patients had a relapse in a year [13]. In a study of S.A. Kramarev, 2008 ($n = 35$) there was a significant decrease in the following clinical symptoms: intoxication, disturbances of the central nervous system, appetite, fever, nasal lesions ($p < 0.05$) after three months of treatment [1]. Data of A.P. Volosovets, 2007 ($n = 35$) show high efficacy of treatment in 30 (85.7%) patients and moderate efficacy in 5 (14.3%) patients with herpes virus infection [20]. After three months of therapy of frequently and chronically ill children (FCIC) infected with herpes viruses who had an often and long disease course, E.I. Yulish et al., 2011, 2013 ($n = 243$) reported a significant (almost 1.5 times) reduction in the incidence of ARVI during the year, and 1.4-fold reduction in the incidence of complications, monitoring (up to 12 months) of FCIC treated with flavonoids showed reduction in the incidence of ARVI in almost three times, reduction of duration of the episode of the disease - 1.5 times, the rate of complications - 35% along with the normalization of immunity [28,29]. In a study of S.A. Kramarev et al., 2014 children showed a decrease of the number and duration of recurrent respiratory diseases, as well as the frequency of complications after treatment with flavonoids [8].

Side effects while using the studied drugs in the described studies are not registered. Also, in the clinical use of drugs the phenomena that require dosage reduction of flavonoids was not observed.

Conclusions

1. This meta-analysis of 30 clinical studies involving 2,699 children with viral, viral and bacterial diseases, with hyperthermia and intoxication syndrome demonstrates the effectiveness and safety of flavonoids (Proteflazidum, Immunoflazidum, Flavozidum) in children.
2. The comparative analysis confirms the prevailing efficacy of these drugs for all investigated characteristics - relief of fever, intoxication syndrome, normalization of leukocytes and lymphocytes, reduction the frequency of relapses.
3. No side effects were found.
4. There were no symptoms of fever during treatment with drugs containing flavonoids.
5. There were no temperature reactions requiring dosage adjustments of the drugs.
6. Clinically significant laboratory abnormalities were not registered during treatment with regimens containing the test substance.

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Meta-analysis of clinical studies on the efficacy of flavonoids in viral and viral-bacterial diseases in children

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Summary. The work shows a meta-analysis of clinical studies of flavonoids effect on the efficiency of reducing fever and intoxication syndrome during viral and viral-bacterial diseases in children. The meta-analysis involving 2,699 children, confirms the efficacy and safety of drugs that contain flavonoids: Proteflazidum, Immunoflazidum, Flavozidum (Ukraine) and proves an anti-relapsing activity of these drugs.

Key words: Proteflazidum, Immunoflazidum, Flavozidum, meta-analysis, viral diseases, children, intoxication syndrome, fever.

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Summary. In the work shows a meta-analysis of clinical studies of the effect of flavonoids on the effectiveness of reducing fever and intoxication syndrome during viral and viral-bacterial diseases in children. A meta-analysis involving 2,699 children, confirms the efficacy and safety of drugs that contain flavonoids: proteflazidum, immunoflazidum, flavozid (Ukraine) and proves an anti activity of these drugs.

Key words: proteflazidum, immunoflazidum, flavozid, meta-analysis, viral diseases, children, intoxication syndrome, fever.

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