Proteflazid®: treatment of herpesvirus and mixed infections. Meta-analysis of clinical trials results

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There is a meta-analysis of clinical trials results concerning the evaluation of efficiency of the drug Proteflazid® (drops) in the treatment of adult patients with herpesvirus and mixed infections.
***Objective of the study:** to evaluate the clinical efficacy of the drug Proteflazid® in a treatment of herpesvirus (HSV-1, HSV-2) and mixed infections in adults by meta-analysis of clinical trials.*
***Materials and research methods.** In meta-analysis, 16 scientific sources with results of controlled studies with participation of 1336 patients over 18 y.o. during 2003-2015 are included.*
***Results.** Obtained data are indicative of efficiency of the drug Proteflazid® in the treatment of patients with herpesvirus and mixed infections. Proteflazid® induces improvement in the main clinical signs of diseases, promotes elimination of herpesviruses from organism and prevention of relapses.*
***Conclusions.** Proteflazid® in the therapy of various clinical forms of HHVs infection promotes the improvement in the main clinical signs of diseases, elimination of HSV-1 and HSV-2; prevention of relapses of diseases (ophthalmoherpes, genital herpes) after completion of the treatment. Therapy of mixed infections (HSV, bacteria, protozoa, fungi) using the drug Proteflazid® promotes improvement in the main clinical signs of diseases, improvement in vaginal mircoflora condition and improvement in local changes in the cervix in women with inflammatory diseases of genital organs as well as in prevention of relapses of genital inflammatory diseases and chronic pyelonephritis.*

Key words: *human herpesviruses infection, mixed infection, Proteflazid®, clinical trials, meta-analysis*

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Proteflazid®: leczenie zakażeń opryszczkowych i mieszanych. Metaanaliza wyników badań klinicznych

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Przedstawiono metaanalizę wyników badań klinicznych pod względem oceny skuteczności preparatu Proteflazid® (krople) przy leczeniu dorosłej kategorii pacjentów z zakażeniami opryszczkowymi i mieszanymi.
***Cel badania:** ocena skuteczności klinicznej preparatu Proteflazid® przy leczeniu zakażeń opryszczkowych (HSV-1, HSV-2) i mieszanych u dorosłych za pomocą metaanalizy badań klinicznych.*
***Materiały i metody badania.** Metaanaliza obejmuje 16 źródeł naukowych z wynikami kontrolowanych badań klinicznych, z udziałem 1336 chorych w wieku ponad 18 lat w okresie od 2003 r. do 2015 r.*
***Wyniki.** Uzyskane dane świadczą o skuteczności preparatu Proteflazid® przy leczeniu chorych posiadających zakażenia opryszczkowe i mieszane. Proteflazid® wywołuje pozytywną dynamikę zasadniczych objawów klinicznych chorób, przyczynia się do usuwania wirusów opryszczki z organizmu oraz profilaktyce występowania nawrotów.*
***Wnioski.** Proteflazid® przyczynia się do pozytywnej dynamiki zasadniczych objawów klinicznych chorób w terapii rozmaitych form klinicznych zakażeń opryszczkowych, do usuwania HSV-1 i HSV-2; do profilaktyki występowania nawrotów chorób (zakażenie opryszczkowe oka, opryszczka narządów płciowych) po zakończeniu kursu leczenia. Terapia zakażeń mieszanych (HSV, bakterie, pierwotniaki, grzyby) z zastosowaniem preparatu Proteflazid® wywołuje pozytywną dynamikę objawów klinicznych chorób, sprzyja poprawie stanu mikroflory pochwy oraz przyczynia się do pozytywnej dynamiki lokalnych zmian szyjki macicy u kobiet z chorobami zapalnymi genitaliów, jak również do profilaktyki występowania nawrotów chorób zapalnych genitaliów oraz przewlekłego odmiedniczkowego zapalenia nerek.*

Słowa kluczowe: *zakażenie opryszczkowe, zakażenie mieszane, Proteflazid®, obserwacje kliniczne, metaanaliza*

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Specific characteristic of the modern infectious pathology is an incidence rate of chronic infectious-inflammatory diseases that form quite enough against the background of persistent human herpesviruses (HHV) infection and mixed infections (herpesviruses in various possible combinations with other microorganisms: bacteria, protozoa, fungi).

Herpesviruses cause a wide variety of clinical forms of infections depending on the site of the pathological process and its prevalence, the condition of the patient's immune system.

HHV infection is caused most often by herpes simplex virus (HSV) – HSV-1 and HSV-2 – antibodies to which are detected in 90-99% of the adult population of the planet. HSV-1 infection usually occurs in the first 3 years of a child's life, and HSV-2 during puberty. According to the WHO, diseases caused by HSV, with regard to the fatality rate due to viral infections, take the second place (15.8%) after the flu (35.8%). Literature data indicate that about 80% of the population is infected by HSV-1, and 10% of women and 15% of men by HSV-2. Ophthalmologists register herpetic keratitis and iridocyclitis in 60% of cases of corneal lesions [28].

HHV infection runs both in the form of a mono- and mixed infection, and in association with viral, bacterial and other infectious agents (mixed infection) which contributes to the potentiation of their pathogenic properties. The leading role of the association of HSV-2 and human papilloma virus in the development of cervical cancer, and prostate cancer has been proved. Association of HSV-2, CMV and toxoplasma has a negative effect on the course of pregnancy and childbirth [12].

The main biological and pathogenetic features of herpesviruses are their lifelong persistence in the body of a person once infected by them, the strongest dependence of the course of the chronic process on the state of the virus carrier immunity and the tendency to recur.

The lifelong persistence of herpesviruses in the human body is due to their unique ability to incorporate their DNAs into the neurons of the regional (in relation to external infection site) ganglia of the sensory nerves of the peripheral nervous system. This way of preserving the parasitic genome in the human body leads to the fact that during the off-recessive period of herpetic infection the immune system that always recognizes only biologically foreign antigens circulating in the body and does not have access to the intracellular spaces "does not see" the DNAs of the herpesviruses and does not react to them, and hence the problem of "detecting" and studying of herpesviruses remains actual [19].

Abnormalities of the immune system play an important role in the persistence of the virus and in the pathogenesis of recurrent herpes. If the immune status is compromised, the herpetic infection becomes more severe with frequent and prolonged relapses which is due to the lack of immunity or an excessive immune response. In turn, herpetic infection causes immunosuppression [21].

The issue of the effective therapy of herpesvirus infection remains in the center of attention of physicians of different specialties due to the annual increase in the number of patients with severe disease and frequent transition to a chronic process. Modern medicine does not have treatment methods that completely eliminate viruses of herpes from the human body. The issue of resistance of viruses to traditional antiviral therapy is also crucial. Presently, effective and safe drugs for the long-term use thereof are sought [15].

One of the most promising agents showing a pronounced direct antiviral effect on DNA-containing viruses, to which the group of herpes viruses belongs, is the proprietary drug Proteflazid® widely used in the clinical practice (SMC Ecopharm Ltd., Ukraine), the active substance of which is obtained from plants *Deschampsia caespitosa* L. and *Calamagrostis epigeios* L. The main biologically active component of the active substance of the drug is a complex compound of O- and C-glycoside flavones: tricin, luteolin, and apigenin.

The drug Proteflazid® is characterized by a number of basic pharmacodynamic properties: etiotropic action: it suppresses virus-specific enzymes of DNA- and RNA-virus synthesis (thymidine kinase, DNA and RNA polymerase, reverse transcriptase) which is accompanied by a decrease in the ability of replication of viral nucleic acids or complete blockade thereof and, as a result, makes it impossible to duplicate DNA and RNA viruses; pathogenetic action: it has an immunotropic mechanism of action – optimizes the synthesis of endogenous á- and ă-interferons (IFNs), restores tissue immunity by increasing the level of secretory immunoglobulin A (sIgA); has an antioxidant mechanism of action – it helps to reduce the activity of lipid peroxidation and increase the activity of antioxidant protection resulting in reduced endotoxicosis and increased resistance of cells and tissues to the damaging effects of free radical oxidation products whose level in the body is increased in most pathological processes, especially in inflammation and infectious damage [14,15,28].

The polypharmacological action of the drug Proteflazid® consisting of direct antiviral, immunotropic and antioxidant actions simultaneously provides etiotropic and pathogenetic effects on both viral and mix infections including undesirable processes in the human body caused by this infection. The above properties of the drug Proteflazid® give rise to its wide application in various fields of medicine for the prevention and treatment of a number of infectious diseases caused by viruses: HSV-1, HSV-2, *Epstein-Barr* virus (EBV), cytomegalovirus (CMV), human papillomavirus, hepatitis, HIV, influenza and ARVI, as well as in the complex therapy of viral-bacterial and fungal infections [1-4,6,14,17, 20].

In clinical studies, it has been shown that, when applied topically, the drug Proteflazid® (suppositories or vaginal tampons with drug solution) restores the protective function of the vaginal and cervical mucosa due to normalization of tissue immunity factors (sIgA, lysozyme and complement component C_3), promotes rapid and effective elimination of the causative agent [2,6,17]. The drug Proteflazid® prevents relapses of the disease and prolongs the period of remission [1,20].

The effective and safe use of the drug Proteflazid® (drops) in the treatment of HHV infection is shown in a number of published meta-analysis and systematic reviews of clinical studies [1,3,4,14,20].

Objective of the study. To evaluate the clinical efficacy of the drug Proteflazid® in the treatment of herpesvirus (HSV-1, HSV-2) and mixed infections in adults by meta-analysis of the clinical studies.

MATERIALS AND METHODS

Information on clinical studies regarding the effectiveness of the use of the drug Proteflazid® in the treatment of HHV infection (mono- and mixed infections) in adult patients was obtained using information retrieval systems on the Internet. In addition, the developer of the drug Proteflazid® (SMC Ecopharm Ltd., Ukraine) provided some reports on the clinical trial results of the drug in the treatment of HHV infection.

At the initial stage of the selection, 23 scientific sources with the results on clinical trials of the effectiveness of the drug Proteflazid® in adult patients with HHV infection (mono- and mixed infections) were identified.

In accordance with the inclusion criteria, 13 publications and 3 clinical reports on the results of controlled clinical trials with regard to effectiveness of the drug Proteflazid® in the treatment of HHV infection and mixed infections involving 1336 patients over 18 y.o. during 2003-2015 were selected for meta-analysis, 7 publications were excluded from meta-analysis.

The list of publications selected and included in meta-analysis is presented in the tab. 1.

Software: To ensure a higher degree of reliability of the results two specialized programs RevMan and SPSS were used.

Inclusion criteria:

Studies that were included in meta-analysis corresponded to the following criteria:

1. Controlled studies provided control or control group and focused on examination of the clinical efficacy of the drug Proteflazid® in the treatment of HHV infection (HSV-1, HSV-2) and mixed infections (HSV, bacteria, protozoa, fungi) in patients over 18 y.o.
2. Mandatory confirmation of clinical diagnosis.
3. Published data on the evaluation of the effectiveness of the drug Proteflazid® are complete.

Studies that did not meet the stated criteria were excluded from meta-analysis.

All patients before the beginning of the treatment and after completion of therapy were thoroughly examined including the generally accepted clinical and laboratory studies, ultrasound, the study of the parameters of cellular and humoral immunity. As the main diagnostic method, the methods of enzyme immunoassay (ELISA) and polymerase chain reaction (PCR) were used.

Meta-analysis of clinical studies was carried out for the following statistically significant indicators:

1. Dynamics of clinical symptoms and manifestations of HHV infection in the adult patients against the background of treatment using the drug Proteflazid®:

– incidence of positive dynamics of clinical symptoms in patients with HHV infection;
– incidence of elimination of HSV-1 and HSV-2 detected using PCR in patients with HHV infection;

2. Dynamics of clinical symptoms and manifestations of mixed infections (HSV, bacteria, protozoa, fungi) in the adult patients against the background of treatment using the drug Proteflazid®:

– incidence of positive effect of the treatment of inflammatory diseases of genitals caused by a mixed infection;
– incidence of improvement in the condition of the vaginal microflora in women with inflammatory diseases of the genitals caused by a mixed infection;

Table 1. The list of selected publications reflecting the effectiveness of the use of the drug Proteflazid® in the treatment of HHV infection and mixed infections in adult patients
Tabela 1. Wykaz wybranych publikacji, odzwierciadlających skuteczność zastosowania preparatu Proteflazid® przy leczeniu zakażeń opryszczkowych i mieszanych u dorosłej kategorii pacjentów

Author	Year	Country	Total number of patients	Application field of the drug Proteflazid®	Clinical trials results
1. Publications reflecting the effectiveness of the use of the drug Proteflazid® in the treatment of HHV infection caused by HSV-1 and HSV-2 in adults					
Petrunya A.M. [24]	2003	Ukraine	47	Keratitis caused by herpesvirus infection	Positive dynamics of clinical indicators, prolongation of disease-free survival, reduction of relapse rate
Lesovoy V.N. [19]	2006	Ukraine	54	Genital herpes	Significant reduction in viral replication, normalization of immunological parameters
Rykov S.O. [26]	2010	Ukraine	134	Keratitis caused by herpesvirus infection	Stabilization of the infectious process, improvement in visual functions, reduction of relapse rate
Klymenko P.M. [15]	2012	Ukraine	40	Urogenital herpes	Improving the effectiveness of therapy, acceleration of the onset of the remission phase, reduction of relapse rate
Kornatskaya A.G. [16]	2015	Ukraine	30	Genital herpes	Significant reduction in clinical manifestations of the disease, reduction of relapse rate
Hopchuk O.M. [9]	2006	Ukraine	70	Genital herpes	A positive therapeutic effect, reduction of relapse rate
Sundukov A.V. [30]	2008	Russian Federation	52	Genital herpes	Significant reduction in clinical manifestations of the disease, reduction of lapse rate, prolongation of inter-relapse period
Zapolskiy M.E. [12]	2012	Ukraine	88	Multiform exudative erythema associated with herpesvirus infection	Improving the function of the immune system, reduction of relapse rate
2. Publications reflecting the effectiveness of the use of the drug Proteflazid® in the treatment of mixed infections in adults					
Romashchenko O.V. [27]	2005	Ukraine	60	Inflammatory diseases caused by mixed infection	Increasing the effectiveness of therapy, reduction of disease of genitals in women relapse rate
Rak L.M. [25]	2013	Ukraine	64	Inflammatory diseases of uterine adnexa caused by mixed infection	Increasing the effectiveness of therapy, reduction of disease relapse rate
Beniuk V.A. [7]	2015	Ukraine	70	Urogenital mixed infection	Significant reduction in clinical manifestations of the disease, reduction of relapse rate
Sidorenko E.V. [29]	2010	Ukraine	195	Chronic pyelonephritis caused by mixed infection	Increasing the effectiveness of complex therapy, reduction of disease relapse rate
Kolesnik M.O. [18]	2014	Ukraine	150	Acute and chronic pyelonephritis caused by mixed infection	Increasing the effectiveness of complex therapy, reduction of disease relapse rate
Shvedyuk S.V. [32]	2003	Ukraine	22	Urogenital clamidiosis coupled with genital herpes	Increasing the effectiveness of therapy, reduction of disease relapse rate
Grinkevich T.M. [11]	2005	Ukraine	120	Genital herpes	Significant reduction in clinical manifestations of the disease, reduction of relapse rate
Bayev A.I. [5]	2011	Kazakhstan	140	Mixed-STIs	Clinical improvement, normalization of immunological and biochemical parameters

– incidence of positive dynamics of local changes in the cervix in women with inflammatory diseases of the genitals caused by a mixed infection.

3. Prevention of the disease relapse after completion of the therapy:
– incidence of ophthalmoherpes relapse;
– incidence of genital herpes relapse;
– incidence of relapse of chronic pyelonephritis caused by mixed infection;
– incidence of relapse of inflammatory diseases of genitals caused by mixed infection.

Clinical test results according to said indicators are provided in tables 2-10.

Table 2. Incidence of positive dynamics of clinical symptoms in patients with HHV infection
Tabela 2. Częstość występowania przypadków pozytywnej dynamiki objawów klinicznych u chorych z zakażeniami opryszczkowymi

Author	Main group		Control group	
	Number of patients treated with Proteflazid® who had a positive dynamics of clinical symptoms	Total number of patients	Number of patients who didn't take Proteflazid® and had a positive dynamics of clinical symptoms	Total number of patients
Shvedyuk S.V., 2003	9	11	8	11
Hopchuk O.M., 2006	29	35	20	35
Lesovoy V.N., 2006	27	30	17	24
Klymenko P.M., 2012	19	30	5	10
Zapolskiy M.E., 2012	31	32	16	26
Kornatskaya A.G., 2015	35	35	35	35
Total	150	173	101	141

According to the indicator "The incidence of positive dynamics of clinical symptoms in patients with HHV infection" against the background of the drug Proteflazid®, 314 patients were examined of which 173 were the main group, and 141 constituted the control group (Table 2).

According to the indicator "The incidence of cases of positive dynamics of local changes in the cervix in women with inflammatory diseases of the genitals caused by a mixed infection" against the background of the drug Proteflazid®, 124 female patients with inflammatory diseases of the genitals caused by a mixed infection were examined of which 62 were the main group, and 62 constituted the control group (Table 6).

Table 3. Incidence of elimination of HSV-1 and HSV-2 detected using PCR in patients with HHV infection
Tabela 3. Częstość występowania przypadków usuwania HSV-1 i HSV-2 ujawniona za pomocą PCR (reakcji łańcuchowej polimerazy) u chorych z zakażeniami opryszczkowymi

Author	Main group		Control group	
	Number of patients treated with Proteflazid® who had a marked elimination of HSV-1 and HSV-2	Total number of patients	Number of patients who didn't take Proteflazid® and had a marked elimination of HSV-1 and HSV-2	Total number of patients
Hopchuk O.M., 2006	29	35	20	35
Lesovoy V.N., 2006	27	30	17	24
Total	56	65	37	59

According to the indicator "The incidence of elimination of HSV-1 and HSV-2 detected using PRC in patients with HHV infection" against the background of the drug Proteflazid®, 124 patients with HHV infection were examined of which 65 were the main group, and 59 constituted the control group (Table 3).

According to the indicator "The incidence of ophthalmoherpes relapse" against the background of the drug Proteflazid®, 147 patients with herpes simplex keratitis and uveitis were examined of which 72 were the main group, and 75 constituted the control group (Table 7).

Table 4. Incidence of positive effect of the treatment of inflammatory diseases of genitals caused by a mixed infection
Tabela 4. Częstość występowania przypadków pozytywnego wpływu na leczenie chorób zapalnych genitaliów spowodowanych przez zakażenia mieszane

Author	Main group		Control group	
	Number of patients treated with Proteflazid® who had a positive effect of the treatment	Total number of patients	Number of patients who didn't take Proteflazid® and had a positive effect of the treatment	Total number of patients
Romashchenko O.V., 2005	25	30	19	30
Bayev A.I., 2011	72	80	43	60
Rak L.M., 2013	28	32	21	32
Beniuk V.A., 2015	34	35	33	35
Total	159	177	116	157

According to the indicator "The incidence of positive effect of the treatment of inflammatory diseases of genitals caused by a mixed infection" against the background of the drug Proteflazid®, 334 patients with inflammatory diseases of genitals caused by mixed infection were examined of which 177 were the main group, and 157 constituted the control group (Table 4).

According to the indicator "The incidence of genital herpes relapse" against the background of the drug Proteflazid®, 272 patients with genital herpes were examined of which 144 were the main group, and 128 constituted the control group (Table 8).

Table 5. Incidence of improvement in the vaginal microflora condition in women with inflammatory diseases of the genitals caused by a mixed infection
Tabela 5. Częstość występowania przypadków poprawy stanu mikroflory pochwy u kobiet z chorobami zapalnymi genitaliów spowodowanymi przez zakażenia mieszane

Author	Main group		Control group	
	Number of female patients treated with Proteflazid® who had a marked improvement in vaginal microflora condition	Total number of female patients	Number of female patients who didn't take Proteflazid® and had a marked improvement in vaginal microflora condition	Total number of female patients
Romashchenko O.V., 2005	25	30	18	30
Hopchuk O.M., 2006	29	35	20	35
Rak L.M., 2013	27	32	19	32
Total	81	97	57	97

According to the indicator "The incidence of cases of improvement in the vaginal microflora condition in women with inflammatory diseases of the genitals caused by a mixed infection" against the background of the drug Proteflazid®, 194 female patients with inflammatory diseases of the genitals caused by a mixed infection were examined of which 97 were the main group, and 97 constituted the control group (Table 5).

According to the indicator "The incidence of relapse of chronic pyelonephritis caused by mixed infection" against the background of the drug Proteflazid®, 345 patients with chronic pyelonephritis were examined of which 145 were the main group, and 200 constituted the control group (Table 9).

According to the indicator "The incidence of relapse of inflammatory diseases of genitals caused by mixed infection"

against the background of the drug Proteflazid®, 124 patients with inflammatory diseases of genitals caused by mixed infection were examined of which 62 were the main group, and 62 constituted the control group (Table 10).

Table 6. Incidence of positive dynamics of the local changes in the cervix in women with inflammatory diseases of the genitals caused by a mixed infection
Tabela 6. Częstość występowania przypadków pozytywnej dynamiki lokalnych zmian szyjki macicy u kobiet z chorobami zapalnymi genitaliów spowodowanymi przez zakażenia mieszane

Author	Main group		Control group	
	Number of female patients treated with Proteflazid® who had a positive dynamics of local changes in the cervix	Total number of female patients	Number of female patients who didn't take Proteflazid® and had a positive dynamics of local changes in the cervix	Total number of female patients
Romashchenko O.V., 2005	6	30	2	30
Rak L.M., 2013	18	32	3	32
Total	24	62	5	62

Table 7. Incidence of ophthalmoherpes relapse
Tabela 7. Częstość występowania przypadków nawrotu opryszczkowego zakażenia oka

Author	Main group		Control group	
	Number of patients treated with Proteflazid® who had ophthalmoherpes relapse	Total number of patients	Number of patients who didn't take Proteflazid® and had ophthalmoherpes relapse	Total number of patients
Petrunya A.M., 2003	2	22	5	25
Rykov S.O., 2010	4	50	22	50
Total	6	72	27	75

Table 8. Incidence of genital herpes relapse
Tabela 8. Częstość występowania przypadków nawrotu opryszczki narządów płciowych

Author	Main group		Control group	
	Number of patients treated with Proteflazid® who had genital herpe relapse	Total number of patients	Number of patients who didn't take Proteflazid® and had genital herpes relapse	Total number of patients
Shvedyuk S.V., 2003	2	11	5	11
Grinkevich T.M., 2005	39	49	45	51
Sundukov A.V., 2008	10	22	24	30
Zapolskiy M.E., 2012	4	32	9	26
Klymenko P.M., 2012	2	30	3	10
Total	57	144	86	128

Table 9. Incidence of relapse of chronic pyelonephritis caused by mixed infection
Tabela 9. Częstość występowania przypadków nawrotu przewlekłego odmiedniczkowego zapalenia nerek spowodowanego przez zakażenia mieszane

Author	Main group		Control group	
	Number of patients treated with Proteflazid® who had chronic pyelonephritis relapse	Total number of patients	Number of patients who didn't take Proteflazid® and had chronic pyelonephritis relapse	Total number of patients
Sidorenko E.V., 2010	14	85	33	110
Kolesnik M.O., 2014	0	60	6	90
Total	14	145	39	200

Table 10. Incidence of relapse of inflammatory diseases of genitals caused by mixed infection
Tabela 10. Częstość występowania przypadków nawrotu chorób zapalnych genitaliów spowodowanych przez zakażenia mieszane

Author	Main group		Control group	
	Number of patients treated with Proteflazid® who had relapse of inflammatory diseases of genitals	Total number of patients	Number of patients who didn't take Proteflazid® and had relapse of inflammatory diseases of genitals	Total number of patients
Romashchenko O.V., 2005	1	30	5	30
Rak L.M., 2013	1	32	5	32
Total	2	62	10	62

RESEARCH RESULTS AND DISCUSSION THEREOF

Dynamics of clinical symptoms and manifestations of HHV infection in the adult patients on the background of the treatment using drug Proteflazid®

Fig. 1 depicts the Forest plot of the results of meta-analysis based on identification of the odds ratio of the incidence of positive dynamics of clinical symptoms in patients with HHV infection after use of the drug Proteflazid® in the main and control groups.

The value of χ-square test (P=0.41) and I^2-test (I^2=0%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. P-value of *Fisher's* ratio test (P = 0.0001) shows significance of the selected effect.

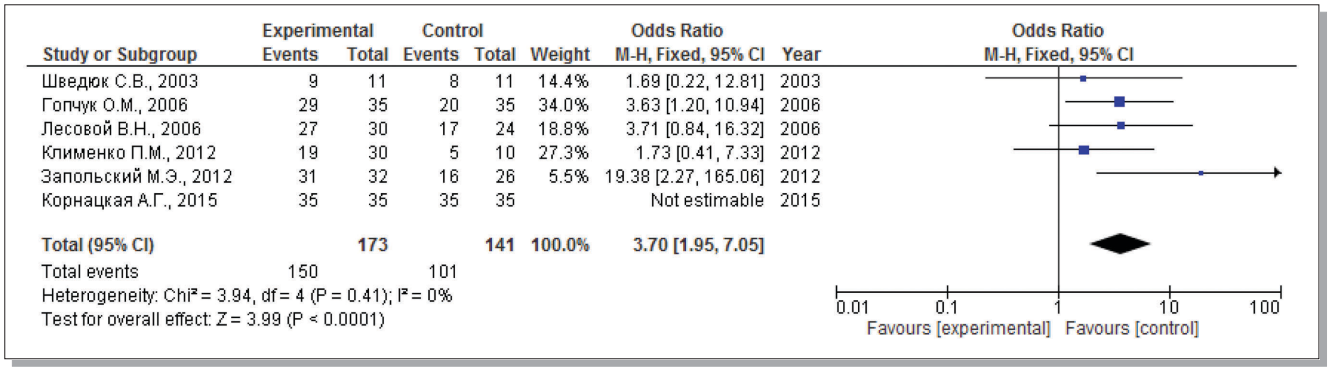

Figure 1. Results of meta-analysis based on identification of the odds ratio of the incidence of positive dynamics of clinical symptoms in patients with HHV infection

Rycina 1. Wyniki metaanalizy na podstawie ustalenia relacji szans częstości występowania przypadków pozytywnej dynamiki objawów klinicznych u chorego z zakażeniem opryszczkowym

The value of odds ratio (OR = 3.70) indicates that the probability of an incidence of positive dynamics of clinical symptoms in patients with HHV infection after use of the drug Proteflazid® in the main group is 3.70 times higher than in the control group.

According to this indicator, the most significant is the study by *Gopchuk O.M.* (2006) which states that the use of the drug Proteflazid® in the complex treatment of herpesvirus genital lesions is more clinically, microbiologically and immunologically effective than traditional methods [9]. A study conducted by *Zapolsky M.E.* (2012) notes that the use of the drug Proteflazid® contributes to a significant decrease in the CIC content (p<0.05), an increase in IgG [12]. *Kornatskaya A.G.* (2015) concludes that the use of the drug Proteflazid® (vaginal tampons with drug solution) promotes an increase in the level of tissue immunity indices (secretory IgA, lysozyme, complement component C_3) [16].

Fig. 2 shows the Forest plot of the results of meta-analysis based on the identification of the odds ratio of the incidence of elimination of HSV-1 and HSV-2 detected by PCR in patients with HHV infection after use of the drug Proteflazid® in the main and control groups.

The value of χ-square test (P=0.98) and I^2-test (I^2=0%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. P-value of Fisher's ratio test (P = 0.004) shows significance of the selected effect.

The value of odds ratio (OR=3.65) indicates that the probability of an incidence of elimination of HSV-1 and HSV-2 detected by PCR in patients with HHV infection after using of the drug Proteflazid® in the main group is 3.65 times higher than in the control group.

The most significant is the research by *Gopchuk O.M.* (2006) which states that therapy with the inclusion of the drug Proteflazid® contributes to a reliable increase in the number of CD4 + lymphocytes and NK cells to normal values, an increase in the amount of IFN-γ and IFN-α [9]. A study conducted by *Lesovoy V.N. et al.* (2006) notes that the drug Proteflazid® increases the positive effect of the therapy by 15-20% [19].

Dynamics of clinical symptoms and manifestations of mixed infection (HSV, bacteria, protozoa, fungi) in the adult patients on the background of the treatment using drug Proteflazid®

Figure 3 depicts the Forest plot of the results of meta-analysis based on identification of the odds ratio of the incidence of positive effect of the treatment of inflammatory diseases of genitals caused by mixed infection after use of the drug Proteflazid® in the main and control groups.

The value of χ-square test (P=0.97) and I^2-test (I^2=0%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. P-value of *Fisher's* ratio test (P = 0.0002) shows significance of the selected effect.

The value of odds ratio (OR=3.28) indicates that the probability of an incidence of positive effect of the treatment of inflammatory diseases of genitals caused by mixed infection after use of the drug Proteflazid® in the main group is 3.28 times higher than in the control group.

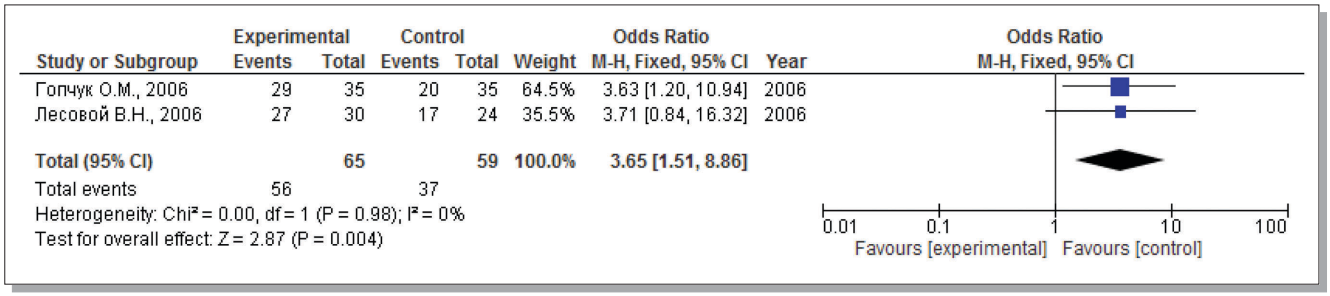

Figure 2. Results of meta-analysis based on the identification of the odds ratio of the incidence of elimination of HSV-1 and HSV-2 detected by PCR in patients with HHV infection

Rycina. 2. Wyniki metaanalizy na podstawie relacji szans częstości usuwania HSV-1 i HSV-2, ustalonej za pomocą PCR u chorych z zakażeniem opryszczkowym

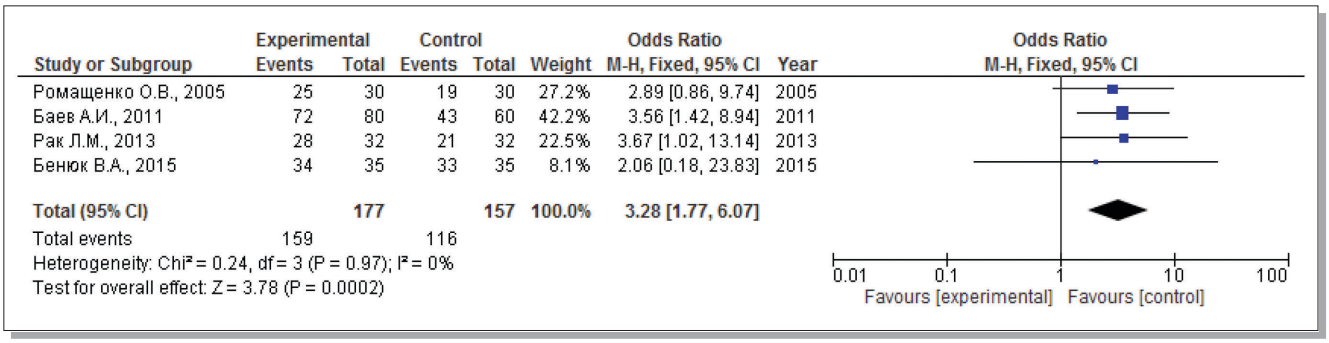

Figure 3. Results of meta-analysis based on identification of the odds ratio of the incidence of positive effect of the treatment of inflammatory diseases of genitals caused by mixed infection
Rycina 3. Wyniki metaanalizy na podstawie ustalenia relacji szans częstości występowania przypadków pozytywnego wpływu na leczenie chorób zapalnych genitaliów spowodowanych przez zakażenia mieszane

The most significant is the study by *Baev A.I. et al.* (2011) who indicate the most significant clinical and immunological changes in the use of the drug Proteflazid®: an increase in the relative percentage of CD3, CD4, CD20-lymphocytes; decrease in CD8-lymphocyte content and CD4/CD8 ratio; normalization of the indices of the main classes of immunoglobulins A, M and G [5]. *Benyuk V.A.* (2015) notes that the evidence of the effectiveness of the therapy with the use of the drug Proteflazid® in both tested groups was a reliable increase in tissue immunity indices. In particular, the level of secretory IgA and the level of lysozyme increased by the 14th day of the treatment remaining significantly high throughout the follow-up period (for secretory IgA: 1641.9 μg/L at the screening, 2154.2 μg/L on the 14th day, 2859.3 μg/L at the end of the 4-week observation, for the lysozyme: 26.7 μg/L at the screening, 48.2 μg/L on the 14th day, 39,0 μg/L at the end of the 4-week observation); level of the complement component C_3 increased in the main group by the 14th day of the treatment and returned to baseline by the end of the 4-week observation period (24.7 μg/g protein at the screening, 33.0 μg/g protein on the 14th day, 24.5 μg/g protein at the end of the 4-week observation for the complement component C_3) [7].

Figure 4 shows the Forest plot of the results of meta-analysis based on the identification of the odds ratio of the incidence of improvement in condition of vaginal microflora in women with inflammatory diseases of genitals caused by mixed infection after use of the drug Proteflazid® in the main and control groups.

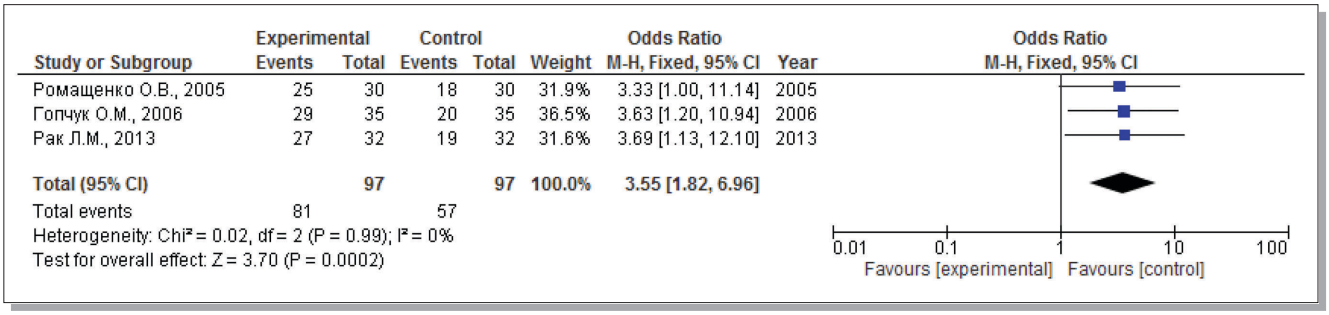

Figure 4. Results of meta-analysis based on the identification of the odds ratio of the incidence of improvement in condition of vaginal microflora in women with inflammatory diseases of genitals caused by mixed infection
Rycina 4. Wyniki metaanalizy na postawie ustalenia relacji szans częstości występowania przypadków poprawy stanu mikroflory pochwy u kobiet z chorobami zapalnymi genitaliów spowodowanymi przez zakażenia mieszane

The value of χ-square test (P=0.99) and I^2-test (I^2=0%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. P-value of Fisher's ratio test (P = 0.0002) shows significance of the selected effect. The value of odds ratio (OR=3.55) indicates that the probability of an incidence of improvement in vaginal microflora condition in wo-

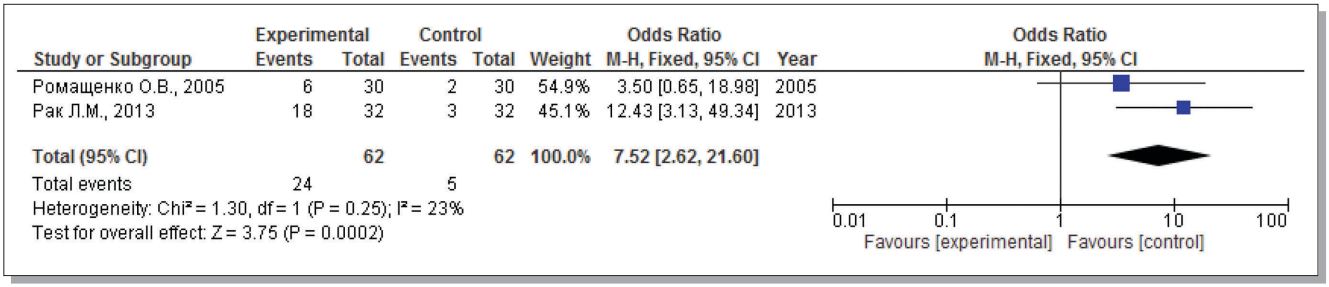

Figure 5. Results of meta-analysis based on the identification of the odds ratio of the incidence of positive dynamics of the local changes in the cervix in women with inflammatory diseases of genitals caused by mixed infection
Rycina 5. Wyniki metaanalizy na postawie ustalenia relacji szans częstości występowania przypadków pozytywnej dynamiki lokalnych zmian szyjki macicy u kobiet z chorobami zapalnymi genitaliów spowodowanymi przez zakażenia mieszane

men with inflammatory diseases of genitals caused by mixed infection after use of the drug Proteflazid® in the main group is 3.55 times higher than in the control group. The most significant is the research by *Gopchuk O.M*. (2006) which notes that the inclusion of the drug Proteflazid® in the complex therapy of herpetic infection in women contributes to the normalization of the vaginal microbiocenosis [9].

Figure 5 shows the Forest plot of the results of meta-analysis based on the identification of the odds ratio of the incidence of positive dynamics of the local changes in the cervix in women with inflammatory diseases of genitals caused by mixed infection after use of the drug Proteflazid® in the main and control groups.

The value of χ-square test (P=0.25) and I^2-test (I^2=23%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. P-value of Fisher's ratio test (P = 0.0002) shows significance of the selected effect. The value of odds ratio (OR=7.52) indicates that the probability of an incidence of positive dynamics of the local changes in the cervix in women with inflammatory diseases of genitals caused by mixed infection after use of the drug Proteflazid® in the main group is 7.52 times higher than in the control group. According to this indicator, the most significant is the study by (*Romashchenko O.V. et al.* who note that the use of the drug Proteflazid® was characterized by the development of marginal and mosaic epithelization of the erosive surface of the cervix by the end of treatment in 8 (26.2%) patients and complete epithelization in 6 (20%) patients [27].

Prevention of disease relapse after completion of the treatment

Figure 6 depicts the Forest plot of the results of meta-analysis based on identification of the odds ratio of the incidence of ophthalmoherpes relapse after use of the drug Proteflazid® in the main and control groups.

relapse of ophthalmoherpes (keratitis, uveitis) after use of the drug Proteflazid® in the main group is 6.25 times lower than in the control group. The most significant is the study by *Rykov S.O. et al.* which proved that inclusion of antiviral and immunocorrecting drug Proteflazid® in the complex therapy for treatment of herpes simplex keratitis allows to decrease the duration of patients care (on average by 4-5 days) and decrease the incidence of relapses by 36% [26]. A study conducted by *Petrunya A.M. et al*. notes that the use of the drug Proteflazid® in a complex therapy and immunorehabilitation of patients with recidivating herpes simplex keratitis contributes to improving of clinical indices, reducing of the incidence of complications of said disease, increasing the duration of disease remission and reducing in the incidence of relapses. Authors conclude that the use of the drug Proteflazid® in patients with herpetic keratitis can be considered pathogenetically valid and reasonable [24].

Figure 7 depicts the Forest plot of the results of meta-analysis based on identification of the odds ratio of the incidence of genital herpes relapse after use of the drug Proteflazid® in the main and control groups.

The value of χ-square test (P=0.79) and I^2-test (I^2=0%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. P-value of Fisher's ratio test (P = 0.0001) shows significance of the selected effect. The value of odds ratio (OR=0.30) indicates that the probability of an incidence of genital herpes relapse after use of the drug Proteflazid® in the main group is 3.33 times lower than in the control group. The most significant is the study by *Sundukov A.V. et al.* who note the high efficacy of the drug Proteflazid® in the treatment of genital herpes that was expressed by significant reduction in the duration of the disease and a significant decrease in the number of relapses [30]. *Shvedyuk S.V. et al.* come to similar conclusions and note that the use of the drug Proteflazid® in patients with genital herpes has contributed to the regression

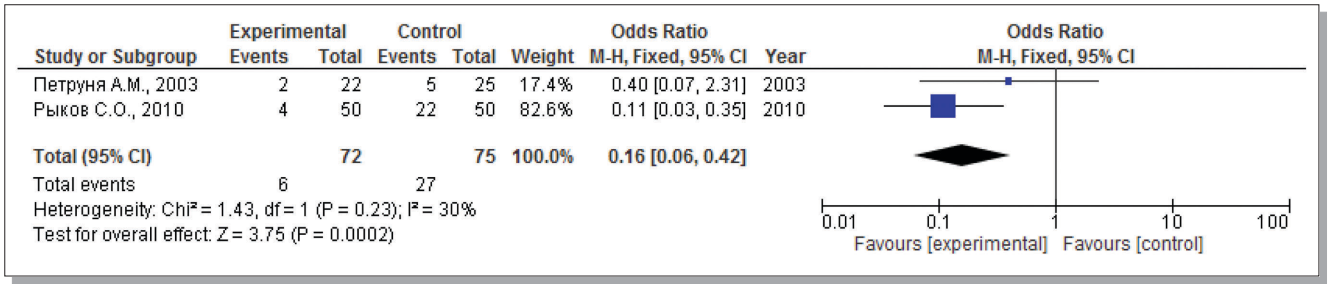

Figure 6. Results of meta-analysis based on identification of the odds ratio of the incidence of ophthalmoherpes relapse
Rycina 6. Wyniki metaanalizy na postawie ustalenia relacji szans częstości występowania przypadków nawrotu opryszczkowego zakażenia oka

The value of χ-square test (P=0.23) and I^2-test (I^2=30%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. P-value of *Fisher's* ratio test (P = 0.0002) shows significance of the selected effect. The value of odds ratio (OR=0.16) indicates that the probability of an incidence of

of clinical symptoms of the disease, the normalization of the vascular pattern of the urethral mucosa, the purification of erosive-ulcerative defects, the disappearance sharp pain during urination [32]. A study by *Klimenko P.M. et al.* indicates that the inclusion of the drug Proteflazid® in the treatment regimen

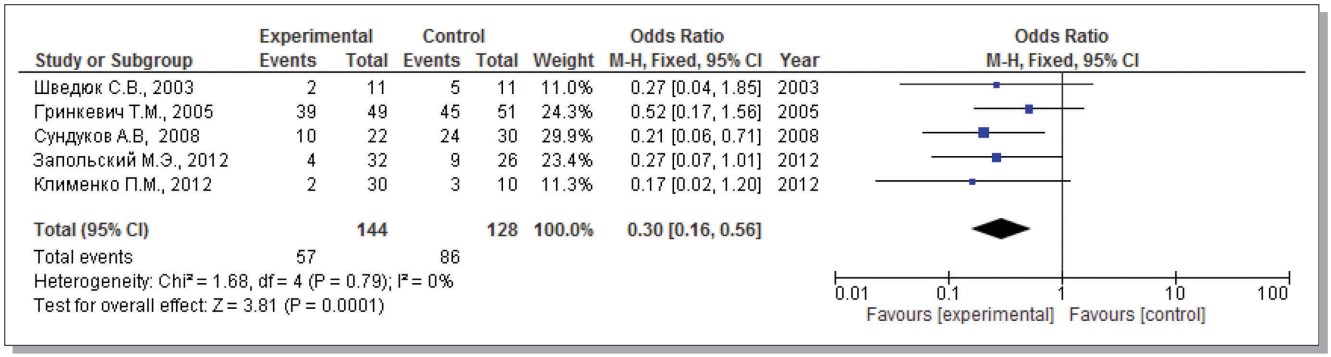

Figure 7. Results of meta-analysis based on identification of the odds ratio of the incidence of genital herpes relapse
Rycina 7. Wyniki metaanalizy na postawie ustalenia relacji szans częstości występowania przypadków nawrotu opryszczki narządów płciowych

made it possible to shorten the genital herpes relapse in patients of the main group by 1.5 times as compared with control group and allowed to reduce the number of relapses by 4.5 times [15].

Figure 8 depicts the Forest plot of the results of meta-analysis based on identification of the odds ratio of the incidence of relapse of chronic pyelonephritis caused by infection after use of the drug Proteflazid® in the main and control groups.

The value of χ-square test (*P*=0.33) and I^2-test (I^2=0%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. *P*-value of *Fisher's* ratio test (*P* = 0.007) shows significance of the selected effect. The value of odds ratio (*OR*=0.40) indicates that the probability of an incidence of relapse of chronic pyelonephritis caused by infection after use of the drug Proteflazid® in the main group is 2.5 times lower than in the control group.

The most significant are two initial studies. *Rak L.M. et al.* note that the incidence of relapse of inflammatory processes of uterine adnexa caused by mixed infection in female patients of control group is 15.6±0.5%, and in female patients that were administered the drug Proteflazid® is 3.1±0.7% (p<0.01) which confirms its clinical effectiveness and the advisability of using in a complex anti-inflammatory therapy in this category of female patients [25]. The study by *Romashchenko O.V. et al.* showed that inclusion of the drug Proteflazid® in the complex therapy of inflammatory diseases of genitals, on the background of HHV infection, in women accompanied with recovery to the normal levels of serum IFN titers, functional activity of phagocytes, indeces of cell and humoral immunity 3 months after treatment completion. 6 months after treatment completion immunity indeces in patients, in the scheme of therapy of which the drug Proteflazid® was included, did not differ from control [27].

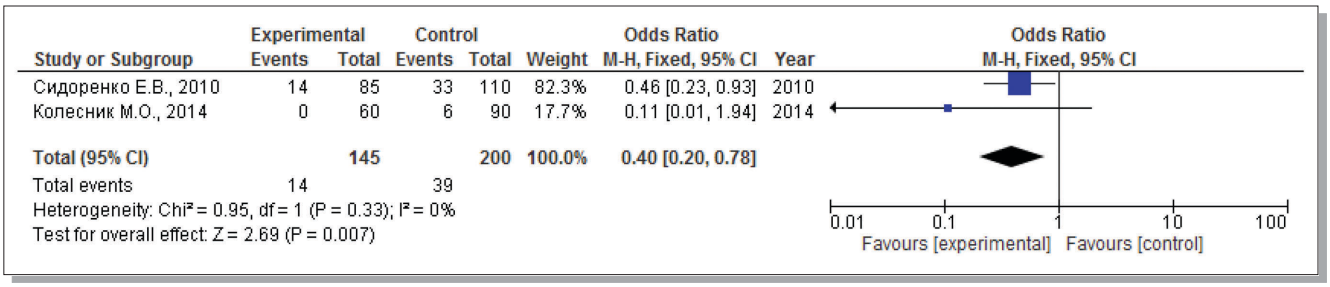

Figure 8. Results of meta-analysis based on identification of the odds ratio of the incidence of relapse of chronic pyelonephritis caused by infection
Rycina 8. Wyniki metaanalizy na postawie ustalenia relacji szans częstości występowania przypadków nawrotu przewlekłego odmiedniczkowego zapalenia nerek spowodowanego przez zakażenia mieszane

The most significant is the research by *Sidorenko E.V.* that notes that the use of the drug Proteflazid® contributes to positive dynamics of clinical condition as well as functional activity of immunocompetent cells and condition of antioxidative system [29]. In their study, *M. Kolesnik et al*. consider that the drug Proteflazid® is a necessary component of the therapy for patients with chronic pyelonephritis, on the background of HHV infection, the use of which prevents the relapses of this disease [18].

Figure 9 depicts the Forest plot of the results of meta-analysis based on identification of the odds ratio of the incidence of relapse of inflammatory diseases of genitals caused by mixed infection after use of the drug Proteflazid® in the main and control groups.

Sensitivity analysis

The sensitivity analysis was carried out in such a way as to evaluate the impact of each individual study as for the combined data omitting an individual study. The results of the sensitivity analysis showed that no single study significantly affected the combined data indicating statistically reliable results.

Assessment of the bias of publications

Funnel plot was used to assess the bias of publications included in the study (fig. 10-18). Virtually all SE values in Figs. 10-18 are within the funnel which indicates that there is no systematic error.

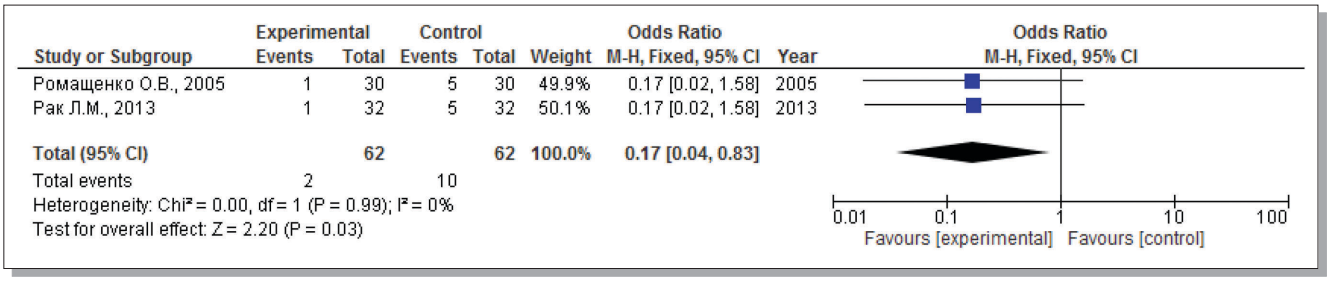

Figure 9. Results of meta-analysis based on identification of the odds ratio of the incidence of relapse of inflammatory diseases of genitals caused by mixed infection
Rycina 9. Wyniki metaanalizy na postawie ustalenia relacji szans częstości występowania przypadków nawrotu chorób zapalnych genitaliów spowodowanych przez zakażenia mieszane

The value of χ-square test (*P*=0.99) and I^2-test (I^2=0%) prove the homogeneity of these studies, therefore a model with a fixed effect is selected. *P*-value of Fisher's ratio test (*P* = 0.03) shows significance of the selected effect. The value of odds ratio (*OR*=0,17) indicates that the probability of an incidence of relapse of inflammatory diseases of genitals caused by mixed infection after use of the drug Proteflazid® in the main group is 5.88 times lower than in the control group.

Conducted meta-analysis allowed to broaden the evidence base regarding the efficacy of the drug Proteflazid® in the treatment of adult patients with herpesvirus (HSV-1, HSV-2) and mixed infections. 16 scientific sources with the results of clinical trials of the effectiveness of the drug Proteflazid® involving 1336 adult patients with HHV infection (mono- and mixed infections) during 2003-2015 were selected. Meta-analysis was conducted according to the following statistically significant criteria:

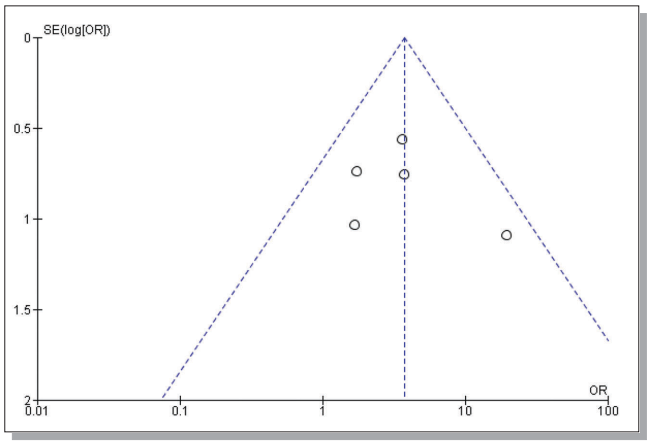

Figure 10. Funnel plot for the indicator "The incidence of positive dynamics of clinical symptoms in patients with HHV infection"
Rycina 10. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków pozytywnej dynamiki objawów klinicznych u chorych z zakażeniem opryszczkowym"

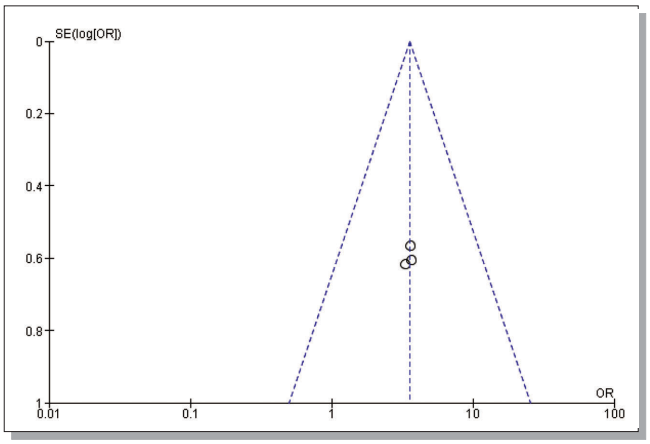

Figure 13. Funnel plot for the indicator "The incidence of improvement in the vaginal microflora condition in women with inflammatory diseases of the genitals caused by a mixed infection"
Rycina 13. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków poprawy stanu mikroflory pochwy u kobiet z chorobami zapalnymi genitaliów spowodowanymi przez zakażenia mieszane"

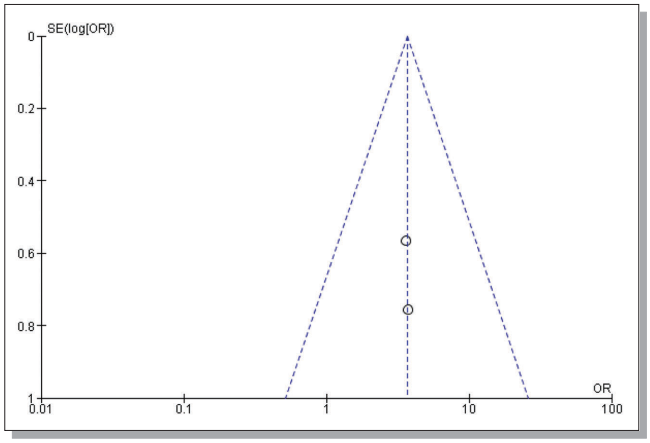

Figure 11. Funnel plot for the indicator "The incidence of elimination of HSV-1 and HSV-2 detected using PRC in patients with HHV infection"
Rycina 11. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków usuwania HSV-1 i HSV-2, ustalona za pomocą PCR u chorych z zakażeniem opryszczkowym"

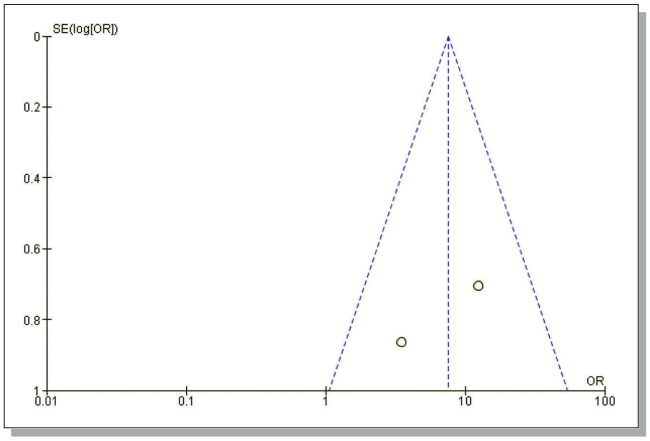

Figure 14. Funnel plot for the indicator "The incidence of positive dynamics of local changes in the cervix in women with inflammatory diseases of the genitals caused by a mixed infection"
Rycina 14. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków pozytywnej dynamiki lokalnych zmian szyjki macicy u kobiet z chorobami zapalnymi genitaliów spowodowanymi przez zakażenia mieszane"

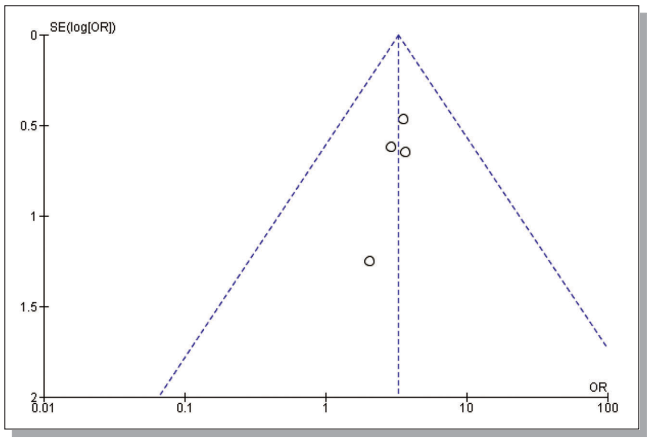

Figure 12. Funnel plot for the indicator "The incidence of positive effect of the treatment of inflammatory diseases of genitals caused by a mixed infection"
Rycina 12. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków pozytywnego wpływu na leczenie chorób zapalnych genitaliów spowodowanych przez zakażenia mieszane"

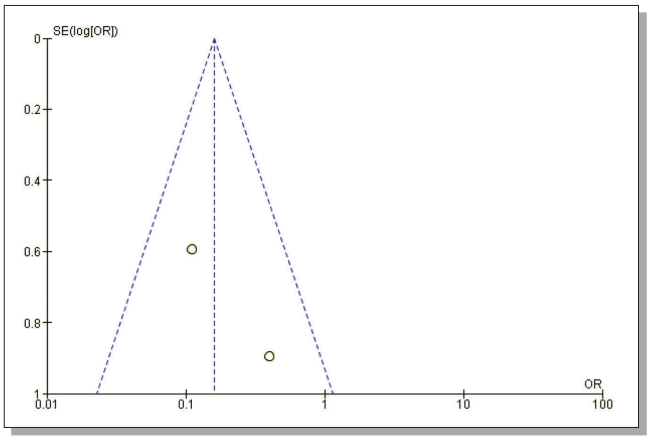

Figure 15. Funnel plot for the indicator "The incidence of ophthalmoherpes relapse"
Rycina 15. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków nawrotu opryszczkowego zakażenia oka"

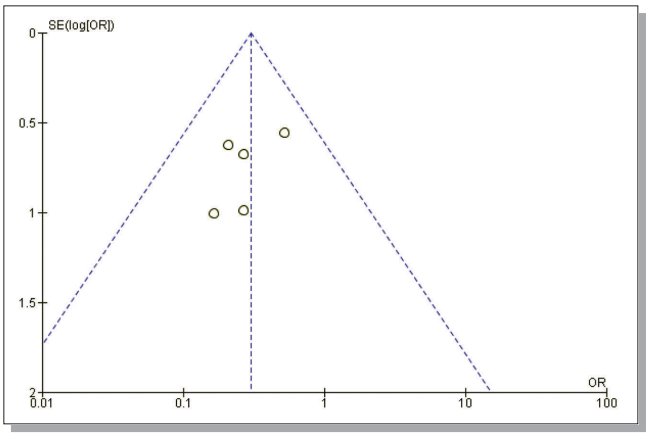

Figure 16. Funnel plot for the indicator "The incidence of genital herpes relapse"
Rycina 16. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków nawrotu opryszczki narządów płciowych"

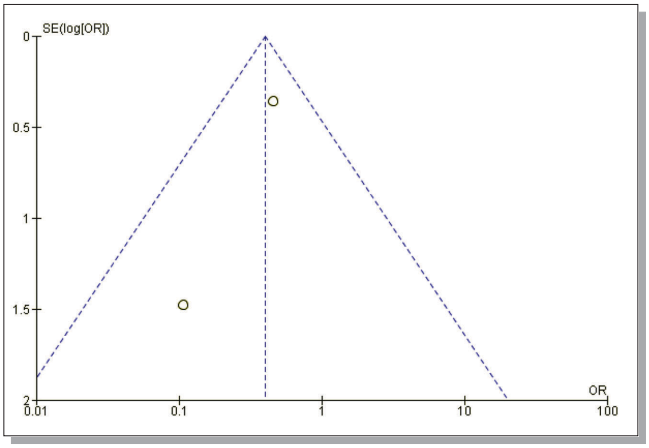

Figure 17. Funnel plot for the indicator "The incidence of relapse of chronic pyelonephritis caused by mixed infection"
Rycina 17. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków nawrotu przewlekłego odmiedniczkowego zapalenia nerek spowodowanego przez zakażenia mieszane"

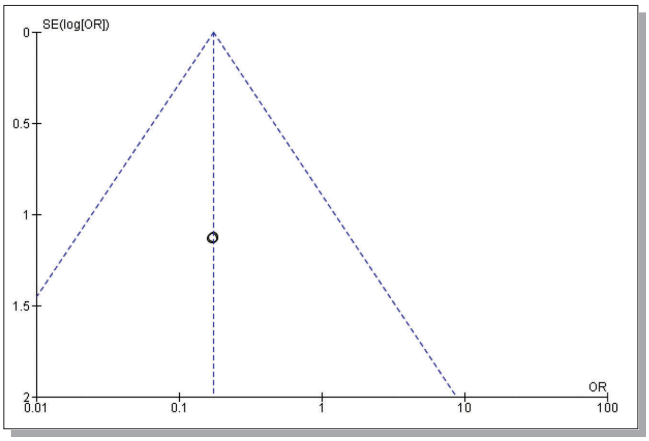

Figure 18. Funnel plot for the indicator "The incidence of relapse of inflammatory diseases of genitals caused by mixed infection"
Rycina 18. Wykres lejkowy typu funnel plot dla wskaźnika „Częstość występowania przypadków nawrotu chorób zapalnych genitaliów spowodowanych przez zakażenia mieszane"

1. Dynamics of clinical symptoms and manifestations of HHV infection in the adult patients against the background of treatment using the drug Proteflazid®:
– incidence of positive dynamics of clinical symptoms in patients with HHV infection;
– incidence of elimination of HSV-1 and HSV-2 detected using PCR in patients with HHV infection.
2. Dynamics of clinical symptoms and manifestations of mixed infections (HSV, bacteria, protozoa, fungi) in the adult patients against the background of treatment using the drug Proteflazid®:
– incidence of positive effect of the treatment of inflammatory diseases of genitals caused by a mixed infection;
– incidence of improvement in the vaginal microflora condition in women with inflammatory diseases of the genitals caused by a mixed infection;
– incidence of positive dynamics of local changes in the cervix in women with inflammatory diseases of the genitals caused by a mixed infection.
3. Prevention of the disease relapse after completion of the therapy:
– incidence of ophthalmoherpes relapse;
– incidence of genital herpes relapse;
– incidence of relapse of chronic pyelonephritis caused by mixed infection;
– incidence of relapse of inflammatory diseases of genitals caused by mixed infection.

CONCLUSIONS

Present meta-analysis confirms the efficacy of drug Proteflazid® in clinical practice in treatment of herpesvirus and mixed infections based on following results obtained.

1. Proteflazid® in patients over 18 y.o. with HHV infection (HSV-1, HSV-2) causes positive dynamics of clinical symptoms of diseases:
– the probability of an incidence of positive dynamics of clinical symptoms in patients with HHV infection after use of the drug Proteflazid® in the main group was 3.70 times higher than in the control group;
– the probability of an incidence of elimination of HSV-1 and HSV-2 detected by PCR in patients with HHV infection in the main group was 3,65 times higher than in the control group.
2. Proteflazid® in patients over 18 y.o. with mixed infection (HSV, bacteria, protozoa, fungi) causes positive dynamics of clinical symptoms of diseases:
– the probability of an incidence of positive effect of the treatment of inflammatory diseases of genitals caused by mixed infection in the main group was 3.28 times higher than in the control group;
– the probability of an incidence of improvement in vaginal microflora condition in women with inflammatory diseases of genitals caused by mixed infection in the main group was 3.55 times higher than in the control group;
– the probability of an incidence of positive dynamics of the local changes in the cervix in women with inflammatory diseases of genitals caused by mixed infection in the main group was 7.52 times higher than in the control group.
3. Proteflazid® in patients over 18 y.o. contributes to prevention of relapses of diseases after treatment completion:
– the probability of an incidence of relapse of ophthalmoherpes in the main group is 6.25 times lower than in the control group;
– the probability of an incidence of genital herpes relapse in the main group was 3.33 times lower than in the control group;
– the probability of an incidence of relapse of chronic pyelonephritis caused by infection in the main group was 2.5 times lower than in the control group;

– the probability of an incidence of relapse of inflammatory diseases of genitals caused by mixed infection in the main group was 5.88 times lower than in the control group.

Meta-analysis of results of clinical trials is indicative of the high efficiency of the drug Proteflazid® (drops) in the treatment of patients over 18 y.o. with herpesvirus (HSV-1, HSV-2) and mixed infections. Proteflazid® in the therapy of various clinical forms of HHV infection promotes positive dynamics of main clinical symptoms of diseases, elimination of HSV-1 and HSV-2; prevention of diseases relapses (ophthalmoherpes, genital herpes) after treatment completion. Therapy of mixed infections (HSV, bacteria, protozoa, fungi) using the drug Proteflazid® promotes positive dynamics of clinical implications of diseases, improvement in vaginal microflora condition and positive dynamics of local changes of the cervix in women with inflammatory diseases of genital organs as well as in prevention of relapses of genital inflammatory diseases and chronic pyelonephritis.

Taking into account the high clinical efficacy, and complex action on various links of virus infection development, the drug Proteflazid® can be recommended as an effective antiviral agent for the treatment of diseases caused by HHV infection (HSV-1, HSV-2) and mixed infections in adult patients.

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