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Evaluation of efficacy of Proteflazid in the treatment of HPV infection: meta-analysis of long-term clinical trials results

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To evaluate the clinical efficacy of Proteflazid in treatment of patients with urogenital diseases and cervical pathology caused by HPV infection a meta-analysis of clinical case-control trials, which involved more than 1,000 patients, was performed. The results showed that Proteflazid eliminates human papillomavirus from the body, prevents the recurrence of the disease, and reduces the risk of virus-induced neoplastic processes.

Keywords: meta-analysis, human papillomavirus, papillomavirus infection, cervical pathology, urogenital diseases, Proteflazid.

Human papillomavirus (HPV) is a widespread and highly variable group of viruses. The problem of diagnosing and treating HPV-associated diseases has been relevant in the past decade due to an abruptly increasing incidence rate, significant contagiousness and high oncogenic potential of the causative agent in various age groups. The target cells for HPV are epithelial skin cells and cells of the mucous membranes. Viruses may cause productive and transforming effects on the epithelium. The productive effect leads to formation of benign neoplasms – papillomas and condylomas of the skin and mucous membranes. The result of the transforming effect is epithelial dysplasia of the cervix, the progressive development of which leads to cervical cancer [15]. While the incidence rate of clinical or advanced cervical cancer is reduced, there is a stable tendency to increase in the proportion of intraepithelial and microinvasive cervical cancer. Most notably, the increase is observed in young women; and the feature of this oncopathology is a short latency period that, according to some authors, is less than 12 months.

Currently, there is a general increase in HPV infection. Thus, the number of patients with papillomavirus infection (PVI) in the last decade has increased by more than 10 times in the world. Since the virus is transmitted sexually, the major peak of infection is observed in young sexually active women. According to various studies, the incidence rate of HPV

infection is 45-81 % in the age group 16-29 years [16]. The spread of this sexually transmitted disease has grown into an epidemic. Cytological features of PVI are diagnosed in 88 % of patients with epithelial dysplasia of the cervix, and the infected cells in 80.2 % of cases are just in the transformation zone, which allows differentiation of surface cervical epithelial cells [27].

Genital PVI is one of the most common infections in the world. Its global incidence rate is 11.7 % (a 95 % confidence interval [CI]: 11.6-11.7). More than 70 types of HPV are the causative agents of human diseases. About 630 million people are infected with HPV on the global scale. In these circumstances, five highly oncogenic HPV genotypes are often identified: HPV-16 (3.2 %), HPV-18 (1.4 %), HPV-52 (0.9 %), HPV-31 (0.8 %) and HPV-58 (0.7 %) [27].

However, these figures reflect only the incidence rate of clinical HPV manifestations but not the true extent of infection in the population since subclinical and latent forms of infection are not recorded.

The course of PVI may involve several stages:

1) Primary infection, when the virus is localized in a limited anatomic region;

2) Persistence of the viral genome in episomal form accompanied by the production of viral particles during the differentiation of epithelial cells (secondary infection is possible at this stage);

3) Oncogenic processes as a result of interaction between viral oncogenes and regulatory proteins of the cell after integration of viral DNA into their genome [17].

Diagnosis of typical PVI manifestations is not difficult, but it is difficult to detect them at early stages. The main diagnostic method of HPV infection is a cytological and histological examination (with detection of koilocytes in a biopsy sample) and the method of polymerase chain reaction (PCR) with identification of the virus type.

A debate over the choice of the most appropriate method of treatment for these patients has been lasting in the literature for more than 30 years. It is inconsistent and non-standardized primarily due to lack of drugs with a direct antiviral effect on HPV. Promising results of the therapy of early-stage tumors with a gradual decrease in the volume of surgical procedures have become a cause to develop a new direction in oncogynecology - organ preservation treatment (E. H. Novikova, 1998) [20].

The current tendency of unjustified and sometimes aggressive treatment of HPV-infected women which has developed in recent years often leads to long-term complications and the disease recurrence.

The current tendency of unjustified and sometimes aggressive treatment of HPV-infected women which has developed in recent years often leads to long-term complications and the disease recurrence. Until recently, there was no specific PVI therapy in the global clinical practice. However, in the course of multiple studies the Ukrainian scientists were able to develop Proteflazid®, a drug with a direct antiviral activity against HPV.

Proteflazid has a specific antiviral activity against HPV. In vitro studies in experimental models of oncogenic HPV demonstrated that the active pharmaceutical ingredient inhibits HPV reproduction by 2 lg ID_{50}. Cytological examinations revealed that Proteflazid inhibited proliferative and destructive effect of HPV on cells. The mechanism of the direct antiviral effect of Proteflazid consists in inhibiting the synthesis of DNA-viruses in infected cells via suppression of activity of virus specific enzymes of DNA polymerase and thymidine kinase.

Proteflazid promotes the synthesis of endogenous α and γ-interferons to a physiologically active level (without the occurrence of refractoriness) which increases non-specific resistance to viral and bacterial infections and normalizes the immune status. The drug also prevents the accumulation of lipid peroxidation products (inhibits free radical processes), and modulates apoptosis, which contributes to the elimination of infected cells.

Clinical studies have shown that Proteflazid applied locally (suppositories and vaginal tampons with a drug solution) helps to restore the protective function of vaginal and cervical mucosa via normalization of local immunity factors (secretory immunoglobulin A, lysozyme and C3-component of complement) [21].

The purpose of the study was to conduct a meta-analysis and evaluate the clinical efficacy of Proteflazid for the treatment of patients with PVI-caused urogenital diseases and cervical pathology.

Materials and methods of the study

Information about clinical studies on the efficacy of Proteflazid in patients with PVI-caused urogenital diseases and cervical pathology has been obtained with the help of information retrieval systems on the Internet. Table 1 shows the list of publications of clinical studies from 2002 to 2015. The basic stages of a meta-analysis are based on conventional methodological and methodical approaches in this field. They summarize the results of several similar studies into a single result and allow to evaluate the treatment efficacy using a much larger sample size than in a separate study.

Software. To ensure a high confidence level of the obtained results, two specialized statistical programs RevMan and Comprehensive meta-analysis were used simultaneously.

Inclusion criteria

The meta-analysis included the studies, which met the following criteria:

1. The study was a case-control study and focused on examining the clinical efficacy of Proteflazid in the treatment of patients with urogenital diseases and cervical pathology caused by PVI.
2. Mandatory confirmation of the clinical diagnosis in all patients with PVI-caused cervical pathology and urogenital diseases.
3. The published data on Proteflazid efficacy are complete.

Table 1. A list of publications reflecting Proteflazid efficacy in the treatment of patients with PVI-caused urogenital diseases and cervical pathology

Author	Year	Country	Total number of patients	Field of Proteflazid administration	Clinical study outcomes
V. H. Radionov [17]	2002	Ukraine	39	Clinical PVI manifestations (condylomas)	A significant decrease in recurrence of condylomatous manifestations
H. A. Vakulenko [20]	2003	Ukraine	599	Cervical pathology	A significant decrease in HPV replication, improved colposcopic picture
V. V. Makahonova [13]	2003	Ukraine	48	Precancerous cervical disease	A significant decrease in HPV replication, improved colposcopic picture
L. M. Malanchuk [4]	2003	Ukraine	22	Cervical dysplasia affected by PVI	A significant regression of dysplasia
O. V. Paliichuk [9]	2004	Ukraine	11	The early stage of cervical cancer	A significant decrease in HPV replication, improved colposcopic picture
I. T. Kishakevych [8]	2004	Ukraine	120	Benign processes of the cervix	A significant decrease in HPV replication, improved colposcopic picture
I. T. Kishakevych [26]	2003	Ukraine	44	Cervical pathology	Full recovery of lysozyme activity of blood serum and cervical content
S. O. Halnikina [2]	2004	Ukraine	356	Pathology of the skin and mucous membranes in women with postovarioectomic syndrome	Elimination of immune system disorders
O. V. Hryshchenko [10]	2005	Ukraine	33	PVI in pregnant women	A significant decrease in HPV replication, absence of recurrences
V. N. Lesovoi [21]	2006	Ukraine	34	Urogenital PVI	A significant decrease in HPV replication, elimination of leucopenia and neutropenia in peripheral blood
N. N. Voloshyna [12]	2007	Ukraine	136	Cervical pathology in pregnant women	A significant decrease in HPV replication
T. V. Herasimova [5]	2007	Ukraine	150	Menstrual disorders caused by viral infection	A significant decrease in HPV replication, improved colposcopic picture

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Continuation of Table 1

Author	Year	Country	Total number of patients	Field of Proteflazid administration	Clinical study outcomes
E. I. Laliantsi [23]	2010	Russian Federation	625	Virus-associated types of urogenital pathology	A significant decrease in HPV replication, regression of cervical dysplasia
O. V. Romashchenko [14]	2010	Ukraine	32	Chronic inflammatory diseases of the genitals complicated by HPV	A significant decrease in HPV replication, regression of cervical dysplasia
M. H. Romaniuk [7]	2011	Ukraine	187	PVI in men	A significant decrease in recurrence of condylomatous manifestations, a significant decrease in HPV replication
N. A. Hodlevska [3]	2012	Ukraine	32	Cervical pathology	A significant decrease in HPV replication, improved colposcopic picture
R. B. Abdiraimova [18]	2013	Kazakhstan	12	Papillomavirus urogenital infection	A significant decrease in HPV replication, elimination of leucopenia and neutropenia in peripheral blood
V. M. Zaporozhan [6]	2014	Ukraine	80	Genital papillomavirus infection	A significant decrease in HPV replication
V. V. Kaminskyi [21]	2015	Ukraine	76	Genital papillomavirus infection	A significant decrease in HPV replication

In accordance with the abovementioned criteria, eight clinical case-control studies were included into the meta-analysis, and 11 were excluded. The study publications covered the period from 2002 to 2015.

From the eight selected studies, the treatment group consisted of 539 patients with PVI-caused urogenital diseases and cervical pathology treated with Proteflazid orally according to the schedule or in the form of local applications and vaginal tampons with a drug solution. The control group consisted of 498 people. In this case, patients in both groups were thoroughly examined before and after the treatment including conventional clinical, laboratory and instrumental examinations, ultrasound pelvic examination, analysis of cellular and humoral immunity, cystoscopy and colpocervicoscopy. PCR method was used as a main diagnostic method with the identification of HPV-16, -18, -31 and -33.

The meta-analysis was conducted in accordance with three parameters:

1. The recurrence rate of condylomatous manifestations.
2. The frequency of HPV detection using PCR method.
3. The rate of disappearance (significant reduction) of HPV replication using PCR method.

According to the recurrence rate of condylomatous manifestations, 106 patients with PVI-caused urogenital diseases and cervical pathology were examined, 65 of which were included into the treatment group and 41 were included into the control group.

According to the frequency of HPV detection using PCR method, 965 patients with PVI-caused urogenital diseases and cervical pathology were examined, 494 of which were included into the treatment group and 471 were included into the control group (Table 2).

Table 2. The frequency of HPV detection using PCR method

Author, year	Treatment group		Control group	
	Number of patients with HPV detected by PCR	Total number of patients	Number of patients with HPV detected by PCR	Total number of patients
V. V. Makahonova, 2003	1	9	5	12
L. M. Malanchuk, 2003	1	12	4	10
V. N. Lesovoi, 2006	2	20	8	14
E. I. Laliantsi, 2010	34	307	96	318
M. H. Romaniuk, 2011	27	108	64	79
V. V. Kaminskyi, 2015	0	38	3	38
Total	65	494	180	471

According to the rate of disappearance (significant reduction) of HPV replication detected by PCR, 1037 patients with PVI-caused urogenital diseases and cervical pathology were examined, 539 of which were included into the treatment group and 498 patients were included into the control group.

Results and discussion

Data integration for analysis

Table 3 shows the statistical data of a meta-analysis based on the odds ratios (OR) of the recurrence rates of condylomatous manifestations.

Figure 1 depicts a forest plot graph with the meta-analysis results based on OR of the recurrence rates of condylomatous manifestations in patients of the treatment and control groups.

The value of χ^2-criterion (P = 0.34) and I^2-test (I^2 = 6 %) indicate that the study data are homogenous. That is why the fixed effects model has been chosen. P-value of Fisher's criterion (P = 0.003) demonstrates the significance of the chosen effect.

The value of OR = 0.18 indicates that the likelihood of the recurrence rate of condylomatous manifestations in the treatment group is 5.5 times lower compared to the control group.

The study of O. V. Hryshchenko et al. (2005) is of utmost importance. They note that the regression of condylomas was shown as a size reduction of masses on the skin and mucous membranes with Proteflazid administration [10]. The analysis of leukograms performed by V. H. Radionov et al. (2002) illustrates the positive effect of Proteflazid on the natural organism resistance in patients of the treatment group [17]. V. N. Lesovoi et al. (2006) indicate that the drug increases the treatment efficacy by 15-17 % and its positive effect is more persistent. Along with this, the risk of transmission of infection to a sexual partner and the risk of virus-induced neoplastic processes are reduced by 47-50 % [21].

Table 4 shows the statistical data of a meta-analysis based on OR of the frequency of HPV detection using PCR method.

Figure 2 depicts a forest plot graph with the meta-analysis results based on OR of the frequency of HPV detection using PCR method in patients from the treatment and control groups.

The value of χ^2-criterion (P = 0.06) indicates the homogeneity and the value of I^2-test (I^2 = 53 %) indicates a minor heterogeneity of the study data. That is why the random effects model has been chosen. P-value of Fisher's criterion (P = 0.00001) demonstrates the significance of the chosen effect.

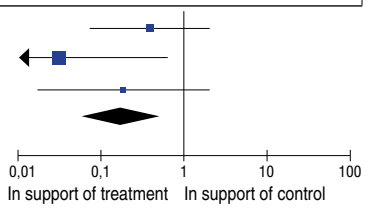
The value of OR = 0.15 indicates that the likelihood of the frequency of HPV detection using PCR method in the treatment group is 6.7 times lower compared to the control group.

The works of E. I. Laliantsi and M. H. Romaniuk are of utmost importance for the study. Specifically, E. I. Laliantsi et.al (2010) found that Proteflazid was highly effective in the treatment of virus-associated vulvovaginal pathology [23]. The clinical study conducted by M. H. Romaniuk et al. (2001) showed the reduction of the rate of carriage of highly oncogenic HPV strains in the course of drug administration [7].

Table 3. Statistical data of a meta-analysis based on OR of the recurrence rate of condylomatous manifestations

Author, year	OR	Lower limit	Upper limit	Standard error
V. H. Radionov, 2002	0.393	0.074	2.077	0.850
O. V. Hryshchenko, 2005	0.032	0.002	0.645	1.537
V. N. Lesovoi, 2006	0.193	0.018	2.089	1.215
Fixed effect	0.211	0.061	0.731	–

Author, year	Groups				Significance, %	OR M-H, Fixed*, 95 % CI	OR M-H, Fixed*, 95 % CI
	Treatment		Control				
	Number of cases	Total	Number of cases	Total			
In support of control	3	24	4	15	29.9	0.39 (0.07; 2.08)	
O.V. Hryshchenko, 2005	0	21	5	12	46.9	0.03 (0.00; 2.09)	
V.N. Lesovoi, 2006	1	20	3	14	23.3	0.19 (0.02; 2.09)	
Total (95 % CI)		65		41	100	0.18 (0.06; 0.56)	
Total cases	4		12				



Heterogeneity: χ^2 = 2.14; df = 2 (P = 0.34); I^2 = 6%

Test for overall effect: Z = 2.94 (P = 0.003)

*Mantel-Haenszel fixed-effect method

Fig. 1. Meta-analysis results based on OR of the recurrence rate of condylomatous manifestations in patients of the treatment and control groups

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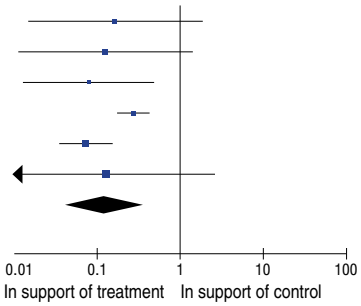
Table 4. Statistical data of a meta-analysis based on OR of the frequency of HPV detection using PCR method

Author, year	OR	Lower limit	Upper limit	Standard error
V. V. Makahonova, 2003	0.175	0.016	1.881	1.212
L. M. Malanchuk, 2003	0.136	0.012	1.513	1.228
V. N. Lesovoi, 2006	0.083	0.014	0.506	0.920
E. I. Laliantsi, 2010	0.288	0.187	0.442	0.219
M. H. Romaniuk, 2011	0.078	0.038	0.159	0.363
V. V. Kaminskyi, 2015	0.132	0.007	2.641	1.530
Random effect	0.145	0.069	0.307	–

Author, year	Groups				Significance, %	OR M-H, Random*, 95 % CI	OR M-H, Random*, 95 % CI
	Treatment		Control				
	Number of cases	Total	Number of cases	Total			
V. V. Makahonova, 2003	1	9	5	12	8.0	0.17 (0.02; 1.88)	
L. M. Malanchuk, 2003	1	12	4	10	7.9	0.14 (0.01; 1.51)	
V. N. Lesovoi, 2006	2	20	8	14	12.2	0.08 (0.01; 0.51)	
E. I. Laliantsi, 2010	34	307	96	318	36.4	0.29 (0.19; 0.44)	
M. H. Romaniuk, 2011	27	108	64	79	30.1	0.08 (0.04; 0.16)	
V. V. Kaminskyi, 2015	0	38	3	38	5.4	0.13 (0.01; 2.64)	
Total (95 % CI)		494		471	100	0.15 (0.07; 0.31)	
Total cases	65		180				

Heterogeneity: Tau² = 0.35; χ^2 = 10.53; df = 5 (P = 0.06); I^2 = 53 %
Test for overall effect: Z = 5.05 (P < 0,00001)



*Mantel-Haenszel random-effect method

Fig. 2 Meta-analysis results based on OR of the frequency of HPV detection using PCR method in patients of the treatment and control groups

V. V. Kaminskyi (2015) found that with Proteflazid therapy dysbiotic states of vaginal microflora resolve; and the local immunity values increase [21].

Table 5 shows the statistical data of a meta-analysis based on OR of the rate of disappearance (significant reduction) of HPV replication using PCR method.

Figure 3 depicts a forest plot graph with the meta-analysis results based on OR of the rate of disappearance (significant reduction) of HPV replication using PCR method in patients of the treatment and control groups.

The values of χ^2-criterion (P = 0.07) and I^2-test (I^2 = 46 %) indicate the homogeneity of the study data. That is why the fixed effects model has been chosen. P-value of Fisher's criterion (P = 0.00001) demonstrates the significance of the selected effect.

The value of OR = 4.68 indicates that the likelihood of the rate of disappearance (significant reduction) of HPV replication using PCR method in the treatment group is 4.7 times higher compared to the control group.

Table 5. Statistical data of a meta-analysis based on OR of the rate of disappearance (significant decrease) of HPV replications using PCR method

Author, year	OR	Lower limit	Upper limit	Standard error
V. H. Radionov, 2002	2.545	0.481	13.458	0.850
V. V. Makahonova, 2003	5.714	0.532	61.410	1.212
L. M. Malanchuk, 2003	2.000	0.324	12.329	0.928
O. V. Hryshchenko, 2005	2.286	0.497	10.503	0.778
V. N. Lesovoi, 2006	12.000	1.976	72.890	0.920
E. I. Laliantsi, 2010	3.472	2.260	5.334	0.219
M. H. Romaniuk, 2011	12.800	6.285	26.067	0.363
V. V. Kaminskyi, 2015	7.592	0.379	152.187	1.530
Fixed effect	4.681	3.346	6.495	–

Author, year	Groups				Significance, %	OR M-H, Fixed*, 95 % CI
	Treatment		Control			
	Number of cases	Total	Number of cases	Total		
V. H. Radionov, 2002	21	24	11	15	4.7	2.55 (0.48; 13.46)
V. V. Makahonova, 2003	8	9	7	12	1.9	5.71 (0.53; 61.41)
L. M. Malanchuk, 2003	9	12	6	10	4.6	2.00 (0.32; 12.33)
O. V. Hryshchenko, 2005	16	21	7	12	5.9	2.29 (0.50; 10.50)
V. N. Lesovoi, 2006	18	20	6	14	2.0	12.00 (1.98; 72.89)
E. I. Laliantsi, 2010	273	307	222	318	67.5	3.47 (2.26; 5.33)
M. H. Romaniuk, 2011	81	108	15	79	12.1	12.80 (6.29; 26.07)
V. V. Kaminskyi, 2015	38	38	35	38	1.3	7.59 (0.38; 152.19)
Total (95 % CI)		539		498	100	4.68 (3.38; 6.49)
Total cases	464		309			

Heterogeneity: $\chi^2 = 12.92$; df = 7 (P = 0,07); $I^2 = 46\%$

Test for overall effect: Z = 9.28 (P < 0,00001)

*Mantel-Haenszel random-effect method

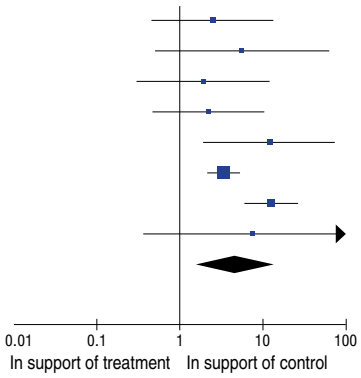


Fig. 3 Meta-analysis results based on OR of the rate of disappearance (significant decrease) of HPV replications using PCR method in patients of the treatment and control groups

The works of E. I. Laliantsi and M. H. Romaniuk are of a great interest. For instance, the study of M. H. Romaniuk et al. (2001) described a decrease in the degree of tissue dysplasia in recurrent condylomas. According to the authors, the combination of the oral course of Proteflazid and the drug solution applied locally is very promising and may lead to the regression of condylomas without surgery [7].

V. V. Makahonova et al. (2003) reported 88.88 % of cases with disappearance of replication of these viruses in the cells of stratified epithelium in HPV-infected female patients on day 21 of Proteflazid therapy; but only 58.34 % of female patients in the comparison group [13]. CO2-laser vaporization of pathological areas led to a complete epithelialization of the cervix confirmed by colposcopy results.

The clinical study of L. M. Malanchuk et al. (2003) showed that dysplasia regression occurred in 60 % of cases in the group taking Proteflazid orally, while in the group where oral administration was combined with vaginal tampons with the drug solution, dysplasia regression occurred in 83.3 % of cases [4]. Therefore, concomitant oral and intravaginal drug administration significantly increases the treatment efficacy.

Sensitivity analysis of the obtained results

Sensitivity analysis was conducted to evaluate the effect of each separate study on the integrated data omitting individual studies. The results of sensitivity analysis showed that no single study affected significantly the integrated data, which is indicative of statistical reliability of results.

Assessment of publication bias

Funnel plot graphs were used to assess publication bias included in the study (Fig. 4-6). Almost all standard error values in Figures 4-6 are within the funnel, which indicates the absence of systematic errors.

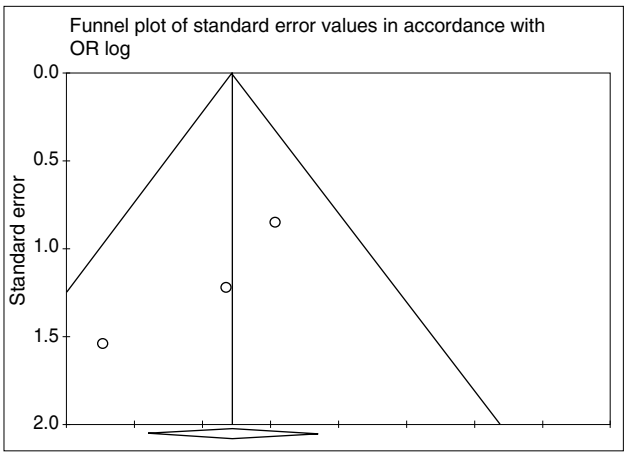


Fig. 4. Funnel plot for the recurrence rate of condylomatous manifestations

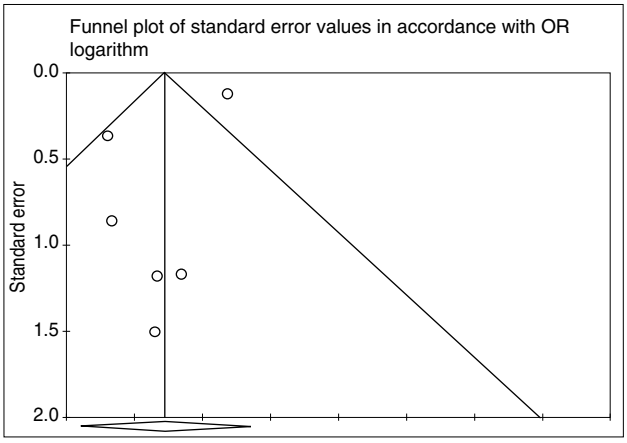


Fig. 5. Funnel plot for the frequency of HPV detection using PCR method

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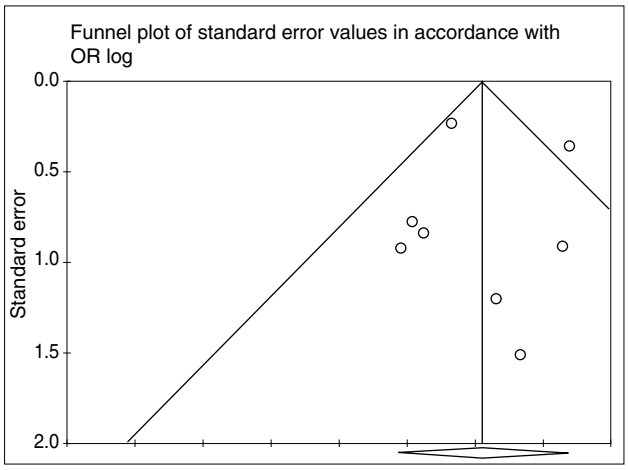

Fig. 6 Funnel plot for the rate of disappearance (a significant reduction) of HPV replication using PCR method.

Conclusions

Meta-analysis showed that: the likelihood of the recurrence rate of condylomatous manifestations in the treatment group is 5.5-fold lower compared to the control group; the likelihood of the frequency of HPV detection (using PCR method) in the treatment group is 6.7-fold lower compared to the control group; the likelihood of the rate of disappearance (significant reduction) of HPV replication using PCR method in the treatment group is 4.7-fold higher compared to the control group.

Thus, the meta-analysis data confirm a high efficacy of Proteflazid in the treatment of patients with PVI-caused urogenital diseases and cervical pathology. Proteflazid eliminates HPV from the body, prevents the recurrence of the disease and reduces the risk of virus-induced neoplastic processes.

Proteflazid in the form of drops and suppositories can be recommended as an effective antiviral agent for the treatment of cervical pathology and urogenital diseases caused by PVI as an etiopathogenetic drug during the acute period, the convalescence period and in HPV persistence.

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Evaluation of efficacy of Proteflazid in the treatment of HPV-infection: meta-analysis of long-term clinical trials results

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To evaluate the clinical efficacy of Proteflazid in treatment of patients with urogenital diseases and cervical pathology caused by HPV infection a meta-analysis of clinical case-control trials, which involved more than 1,000 patients, was performed. The results showed that Proteflazid eliminates human papillo-mavirus from the body, prevents the recurrence of the disease, reduces the risk of virus-induced neoplastic processes.

Keywords: meta-analysis, human papillomavirus, papillomavirusal infection, cervical pathology, uro-genital diseases, Proteflazid.