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EFFICIENCY ASSESSMENT OF COMPLEX TREATMENT OF ANAL CONDYLOMATOSIS

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Цель. Оценить клиническую эффективность комбинированного метода лечения анального кондиломатоза, основанного на применении лазерной деструкции опухолей и иммуномодулирующей терапии.

Материалы и методы. Исследование реализовано в два этапа. В начале проведен ретроспективный сравнительный анализ результатов лечения 60 пациентов с использованием методов лазерной и электрохирургической деструкции анальных кондилом без иммуномодулирующей терапии. Изучались длительность эпителизации ран, частота наступления рецидива. Во втором, проспективном, исследовании у 60 пациентов физические методы деструкции кондилом дополнены терапией в виде человеческого рекомбинантного интерферона α2b и препарата имиквимод.

Результаты. Согласно полученным в ходе исследования данным, лазерная и электрохирургическая деструкция являются эффективными методами лечения аногенитального кондиломатоза. Лазерная деструкция характеризовалась более ранней эпителизацией кожной раны (ANOVA, p=0,00001) и меньшим числом рецидивов заболевания в ближайшие два года наблюдения (Pearson's chisquare test, p=0,0270). При применении только методов физического воздействия отмечено значительно большее количество рецидивов в сравнении с комплексным подходом, при котором лазерная и электрохирургическая деструкция дополнены иммуномодулирующим и противовирусным лечением в виде применения человеческого рекомбинантного интерферона α2b и препарата имиквимод (Cochran Qtest, p = 0,022378). Временной интервал без прогрессирования заболевания в группе пациентов с иммуномодулирующей терапией был значительно дольше, чем в других группах (Kaplan-Meier test, p=0,01528).

Заключение. Результаты исследования позволяют утверждать, что использование лазерного излучения для деструкции анальных кондилом имеет ряд преимуществ перед электрокоагуляцией: более низкий риск развития рецидива, меньшие сроки наступления эпителизации раны. Применение иммуномодулирующей терапии в виде человеческого рекомбинантного интерферона α2b и местного использования препарата имиквимод эффективно дополняет физические методы деструкции кондилом, что позволяет достоверно снижать частоту рецидива заболевания.

Ключевые слова: кондиломатоз, аногенитальные бородавки, лазерная, электрохирургическая деструкция, интерфероны, имиквимод

Objective. To evaluate the clinical efficacy of the combined method of anal condylomatosis treatment, based on laser tumor destruction and immunomodulatory therapy.

Methods. The study included 2 stages. At the first retrospective stage the analysis of 60 patients with anal condylomatosis treatment using laser and electrosurgical destruction methods was performed, immune therapy was not used. The duration of the wound epithelialization, recurrence rate were studied. In the second, prospect study 60 patients were observed; the physical methods of condyloma destruction were supplemented with the therapy of human recombinant interferon α2b and imiquimod.

Results. According to the data obtained during the study, laser and electrosurgical destruction are effective methods of anal condylomatosis treatment. Laser destruction has certain advantages: higher epithelialization rate in the area of exposure (ANOVA, p=0.00001) and fewer recurrences of the disease in terms of 2 years' follow-up (Pearson's chi-squared test, $\chi 2 = 4.89$; p=0.0270). The separate use of physical methods in the treatment of this pathology leads to a much greater number of relapses compared with the complex approach, where laser and electrocoagulation destruction is supplemented with immune and antiviral treatment by human recombinant interferon α2b and imiquimod (Cochran's Q test, Q=9.591549, p = 0.022378). Also the time interval without the disease progressing was longer in this groups (Kaplan-Meier test, p=0.01528).

Conclusions. The results of the study allow us to state that the use of laser radiation for the destruc-

tion of anal condylomas has several advantages over electrocoagulation: a lower risk of recurrence, a shorter period of epithelialization of the wound. The use of immunomodulatory therapy with human recombinant interferon α2b and topical application of imiquimod significantly reduces the frequency of the disease recurrence.

Keywords: condylomatosis, anogenital warts, laser, electrosurgical destruction, interferons, imiquimod

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Научная новизна статьи
Доказано, что использование лазерного излучения в качестве источника физической деструкции анальных кондилом имеет ряд преимуществ перед электрокоагуляционным воздействием. Продемонстрировано, что применение человеческого рекомбинантного интерферона α2b и местное использование препарата имиквимод могут дополнять физический метод лазерной деструкции кондилом и позволяют снизить риск рецидива заболевания.

What this paper adds
It has been proved that the use of laser radiation as a source of physical destruction of anal condyloma has a number of advantages over electrocoagulation. It has been demonstrated that the use of human recombinant interferon α2b and topical use of imiquimod can supplement the physical method of laser destruction of genital condyloma and reduce the risk of recurrence of the disease.

Introduction

Anogenital condylomatosis is characterized by the appearance in a patient of benign tumorous formations in the region of the anus, perineum, genital organs caused mainly by 6 and 11 types of human papillomavirus (HPV) [1, 2]. The virus genome is a circular DNA molecule encoding two types of proteins: early proteins (E-proteins) that determine regulatory functions and virus multiplication, including oncogenic properties due to E6 and E7 proteins, and late proteins (L-proteins) entering in the composition of the virion capsid. The virus attacks keratinocyte progenitor cells in the region of the basal membrane, the replication and release of viral particles occurs in keratinocytes that have reached the terminal stage of differentiation [3]. Therefore, the absence in a patient of exophytic neoplasms of papillomavirus origin does not indicate the elimination of the virus. The prevalence of anogenital condylomatosis reaches 22 cases per 100,000 population, with the average age of patients in economically developed countries ranging from 20 to 28 years [4, 5]. The high prevalence of the disease among the young working-age population of the developed countries determines the social and medical importance of pathology [6].

According to the classification by J. Handley and W. Dinsmoke (2001), several clinical forms are distinguished in case of affection with human papillomavirus of the anogenital region [7]:

– forms with clinical manifestations: warts (condyloma, flat warts, vulgar warts), intraepithelial neoplasia, dyskeratosis, in the absence of dysplasia (flat warts);

– forms with subclinical course: asymptomatic intraepithelial neoplasia, dyskeratosis in the absence of dysplasia (flat condylomas);

– virus-carrying – hidden forms.

Subclinical forms are an asymptomatic lesion of the epithelium, which is determined only by molecular-biological methods of diagnosing the tissue scarification. Patients' diagnosis is made based on complaints and clinical examination data. To verify the virus in clinical practice, amplification methods of laboratory diagnostics are used more often, where the polymerase chain reaction is the most widespread and available method.

For the removal of anogenital warts, the following methods are most often used in health care institutions of the Republic of Belarus: electrosurgical removal, laser destruction, cryodestruction, application of chemical compounds, mechanical excision of formations [8,9]. The rating of methods on the basis of popularity and frequency of use by physicians in outpatient practice in the Republic of Belarus is led by electrosurgical and laser destruction of genital warts.

Using laser radiation to affect soft tissues of the perianal region and the genital area, according to various studies, in comparison with other sources of thermal exposure, permits to reduce energy penetration, which reduces undesirable damaging effects on deeper tissues and is characterized by a lower level of postoperative pain syndrome, edema, as well as a lower risk of postoperative complications [8, 10].

From the point of view of etiology and pathogenesis of the disease, it is advisable to supplement the invasive methods of treatment with immunomodulating and nonspecific antiviral therapy, which is reflected in some foreign reports and clinical recommendations [11, 12]. Currently, a large number of immunocorrecting local and systemic

drugs have been developed. For the treatment of genital warts, the most promising direction is the use of human recombinant interferons [11] and imiquimod drugs [12,13]. Imiquimod is a derivative of imidazoquinolinamine. It is a modulator of an immune response that does not have direct antiviral or antiproliferative effects in vitro, but it stimulates the secretion of interferons, tumor necrosis factor and other cytokines. Interferons are naturally occurring proteins-messengers and have antiviral and antiproliferative activity. In the world practice, for the treatment of various diseases, three types of human interferons are currently used, however, for the treatment of genital warts in the perianal region, the most effective is the use of interferons 2b [11].

Objective. To evaluate the clinical efficacy of the combined method of anal condylomatosis treatment based on laser tumor destruction and immunomodulatory therapy.

Methods

The treatment results of 120 patients with anal condylomas in Minsk, Minsk and Vitebsk regions for the period from 2012 to 2016 have been analyzed. It was revealed that in 98% of cases the doctors used electrocoagulation or laser destruction of neoplasms as the main and only method of treatment. To assess the effectiveness of this tactic, a two-stage study was performed in four clinical groups.

At the first (retrospective) stage of the multicentre study, the therapy results of 60 patients with perianal condylomas being treated at 3rd City Clinical Hospital named after E.V. Klumov, 11th City Clinical Hospital, Vitebsk Regional Clinical Center, LLC "Medandrovit". The patients of the first group (group A, 30 people) underwent laser destruction, the patients of the second group (group B, 30 people) underwent electrosurgical destruction of the condyloma under local anesthesia. The inclusion criterion is the presence of perianal condylomas in patients. Exclusion criteria: the previous stages of treatment for condylomatosis, as well as allergic reactions to local anesthetics, pregnancy, lactation and other standard contraindications for surgical intervention. The frequency and timing of the recurrence onset of the disease, the timing of epithelialization of burn skin wounds were analyzed.

In the second (prospective) study, 60 patients with condylomas of the perianal region participated, who were also divided into two groups by the method of simple randomization-assigning to each of 60 patients a number that is a random number from the table of random numbers, and also by ranking these numbers in ascending order and according to the chosen treatment method: even numbers in the ranked row - group C, odd - group D.

Stratification for the duration of the disease or its severity has not been carried out. Criteria for inclusion and exclusion were the same as for patients in the first stage of the study. Patients of group C (30 people) underwent laser destruction of tumors, patients of group D (30 people) - electrosurgical destruction of condylomas. Interventions were performed under the local infiltration anesthesia. In all groups for laser destruction, radiation with a wavelength of 1.56 m and a power of 10 W in continuous mode was used. For electrosurgical destruction, a high-frequency electrosurgical unit was used in the mode of monopolar coagulation with a power of 25 W. All surgical procedures performed in this study were outpatient and did not require hospitalization of patients.

Patients in groups C, D in the preoperative period were administered the recombinant human interferon 2b at a dose of 1,000,000 units rectally 2 times a day for 10 days. Patients of Group C in the postoperative period were given imiquimod in the form of 5% cream topically after epithelialization of wounds 3 times a week for 4 weeks' period.

Examinations of patients in the postoperative period were carried out at 3, 6, 12 and 24 months (control points).

Data on the age, field and duration of the disease of patients by groups are given in Table 1. No statistically significant differences between groups A, B and also groups C, D were detected by these parameters ($p>0.05$).

Table 1

Separate statistical indicators in groups

Statistical indicators	Group A	Group B	Group C	Group D
Method of treatment	Laser destruction	Electrocoagulation	Laser destruction + interferon + imiquimod	Electrocoagulation + interferon
Average age (M±SD), years	28.6±4.95	29.2±4.66	31.1±5.14	28.7±3.59
Sex ratio: M:W	2.32:1.00	1.72:1.00	2.00:1.00	2.75:1.00
Average duration of the disease, months (median / quartile)	12.00 (Q_{25}= 12.00; Q_{75}= 12.00)	12.00 (Q_{25}= 6.00; Q_{75}= 12.00)	6.00 (Q_{25}= 4.00; Q_{75}= 8.00)	6.00 (Q_{25}= 6.00; Q_{75}= 12.00)

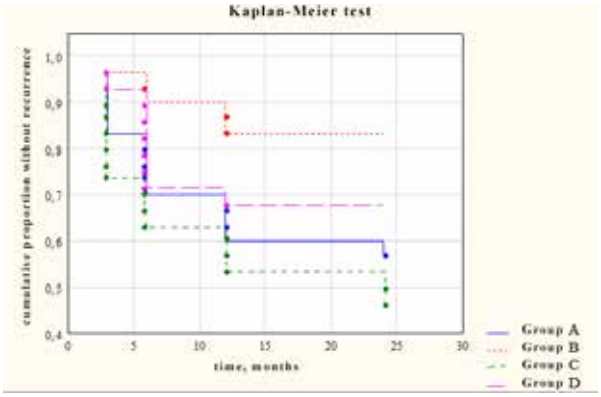
Statistics

The analysis of the obtained data was carried out on a personal computer using the package of licensed programs Statistica (version 6-Index, StatSoft Inc., USA, license number AXXR012E829129FA, serial number NXM12EU007224005571601) and Microsoft Excel 2010 (version 14.0.6129.5000, serial number 02278-001-0000106- 38272) for Windows XP. The hypothesis testing of the distribution normality of the investigated features was tested using the Shapiro-Wilk W test. Depending on the nature of the distribution, the descriptive statistics is represented by arithmetic mean and standard deviations for the normal distribution, and the median and quartiles for distributions that differ from the normal distribution. To analyze the conjugacy tables in independent groups, the Pearson's chi-square test was used, and the Cochran's Q test was used for comparisons of multiple dependent groups. The statistical significance of the differences between the indices of normally distributed independent samples under the condition of multiple comparisons was estimated using the analysis of variance (ANOVA), in the absence of a normal distribution, the Kruskal-Wallis test was used. In the presence of censored data, the Kaplan-Meier test was used.

Results

When analyzing the data obtained during the retrospective stage of the study, it was established that the progression of the disease after surgical treatment using "high energy" sources without concomitant immunocorrection was observed in 41% of cases. In group A, where the laser destruction of genital warts was performed, 10 cases (33%) of the disease progression were recorded during the two-year follow-up, which is significantly less than in group B (electrocoagulation), where 15 cases of disease progression (50%) were recorded (Pearson's chi-square test, p=0.0270).

Fig. 1. Time parameters of the recurrence onset and progression of the disease.



During the second (prospective) part of the study, surgical treatment was supplemented with immunomodulatory therapy. As a result, during the two-year follow-up, the number of cases of the disease recurrence in patients of all groups was distributed as follows: in group A – 10 cases were recorded, group B – 15 cases, group C – 5 cases and group D – 13 cases.

Thus, in a group where the laser destruction of condyloma was supplemented with immunomodulatory therapy (use of recombinant human interferon 2b and imiquimod-group C), there were significantly fewer relapses than in other groups (Cochran's Q test, Q=9.591549, p = 0.022378).

In addition to the fact of disease progression, an important parameter of the effectiveness of treatment is the length of the time interval between the completion of the therapy course and the moment of the recurrence onset. A comparison of the time parameters of the onset of recurrence or progression of the disease in patients of all four study groups revealed that during the two-year period in group C, where laser vaporization with immunomodulatory therapy was performed, the time interval without progression was significantly greater than in the other groups (Kaplan-Meier test, p=0.01528) (Fig. 1).

A significant factor in determining the effectiveness of treatment, affecting the clinical outcome and quality of patient's life in the postoperative period, is the healing time of the postoperative wound. To estimate this index, the variance analysis (ANOVA) was used in patients of all groups (Fig. 2.)

From the data obtained from the analysis it follows that the epithelialization of the wounds occurred earlier in patients in those groups where the laser destruction of genital warts was performed (group A – 2.62 weeks, group C – 3.73 weeks) than in patients who underwent electrocoagulation of the genital warts (group B – 5.17 weeks, group D - 4.73 weeks). When comparing this indicator in a prospective study (in groups C and D), the differences were significant (ANOVA, p = 0.00001).

Discussions

One of the most important indicators of modern methods of treatment, along with safety, is the low risk of recurrence or progression of the disease. The data obtained as a result of a retrospective study (rather high (41%) level of recurrence of clinical forms of anal condylomatosis after performing thermal destruction of formations without the use of concomitant immune therapy) correspond to other known literature data and confirm the theory of the persistence of the virus, as well as probable difficulties of complete damage to the tissues affected by the virus, as well as the presence of unrecognized (subclinical) forms of the disease [2, 4, 7, 8, 12].

The data obtained as a result of the second (prospective) part of the study indicate that in the group where the genital warts were supplemented with immunomodulatory therapy with preparations of recombinant human interferon 2b and imiquimod, significantly fewer relapses were recorded.

The data obtained are also not unexpected, since the effectiveness of laser radiation, as well as the use of immune preparations for the treatment of anogenital warts, has been noted in numerous studies published earlier, and the use of a cream containing imiquimod is fully included in the standards of the European protocols for the treatment of diseases associated with the human papillomavirus , as well as sexually transmitted infections, imiquimod was also approved by the American Medical Conciliation Conference on Infections, transmitted sexually in 2002 [2, 8, 10, 11, 13].

Since the comparison of the results obtained in the retrospective study cannot be regarded as reliable, it is incorrect to discuss the almost double advantage of laser destruction over the electrocoagulation of genital warts as a result of the timing of the onset of epithelialization of the wound. However, significant differences in this indicator were noted in a prospective study.

Conclusions

The results of the research allow us stating that the use of laser radiation as a source of physical destruction of anal warts has several advantages over electrocoagulation: a lower risk of recurrence, a shorter period of epithelialization of the wound. However, the persistence of the virus, as well as the presence of subclinical forms of the disease requires the use of an integrated approach using immunomodulatory and antiviral therapy. The use of human recombinant interferon 2b and topical use of imiquimod may supplement the physical method of laser destruction of genital warts, which allows reducing the risk of the disease recurrence.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethics Committee approval

The work was carried out in accordance with ethical standards, discussed at a meeting of the Committee on the Ethics of Scientific Research of the Belarusian Medical Academy of Post-Graduate Education (Protocol No. 2 of February 14, 2016).

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