UDC 618.146-006:615. 849.19.

MODERN ASPECTS OF PHOTODYNAMIC THERAPY IN GYNECOLOGY: MODERN TACTICS OF TREATMENT OF CERVICAL DISEASES

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✓ ***Resume***

The article is devoted to a comprehensive approach to the treatment of laser photodynamic therapy for cervical diseases. It is shown that laser photodynamic therapy is characterized by shorter epithelialization periods compared to the diathermosurgical method.

Key words: cervix, laser photodynamic therapy, epithelization, conization, coagulation.

СОВРЕМЕННЫЕ АСПЕКТЫ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ В ГИНЕКОЛОГИИ: СОВРЕМЕННАЯ ТАКТИКА ЛЕЧЕНИЯ ЗАБОЛЕВАНИЙ ШЕЙКИ МАТКИ

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✓ ***Резюме***

Обзорная статья посвящена комплексному подходу к лечению лазерной фотодинамической терапии при заболеваний шейки матки. Показано, что лазерная фотодинамическая терапия характеризуется более короткими сроками эпителизации по сравнению с диатермохирургическим методом.

Ключевые слова: шейки матки, лазерная фотодинамическая терапия, эпителизация, конизация, коагуляция.

ГИНЕКОЛОГИЯДА ЛАЗЕР ФОТОДИНАМИК ДАВОЛАШНИНГ ЗАМОНАВИЙ ХУСУСИЯТЛАРИ: БАЧАДОН БЎЙНИ КАСАЛЛИКЛАРИНИ ЗАМОНАВИЙ ДАВОЛАШ

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✓ ***Резюме***

Мақола бачадон бўйни касалликларини даволаш учун лазер фотодинамик даволаш усулига кенг қамровли ёндашув багишланган. Лазер фотодинамик даволаш диатермохирургик усулига нисбатан қисқа эпителиализацион муддатлари билан характерланиши кўрсатилган.

Калит сўзлар: бачадон бўйни, лазер фотодинамик даво, эпителизация, конизация, коагуляция.

Relevance

Photodynamic therapy (PDT) is a new promising treatment method combining the use of a photosensitizer (FS) and low-intensity laser radiation, the wavelength of which corresponds to the peak of absorption of this FS. The essence of the method consists in the occurrence of photosensitized reactions, accompanied by the generation of singlent oxygen and free radicals, a sufficient concentration of which leads to cell death. This method provides selective death of pathological cells, which is ensured by the selectivity of FS accumulation in pathological tissue and local light supply

[1,2,3,5]. Initially, the PDT method was developed and applied in the treatment of malignant neoplasms of the skin, since the cells of malignant neoplasms are the best way to carry out selective accumulation of FS. However, currently there is a search for the use of PDT in a number of non-tumor diseases accompanied by cell proliferation. For the first time, the chemical photosensitization of living tissues by light was observed by Fr .Raab in 1897-1898, the phenomenon of the death of paramecia in an environment with acridine dye under the influence of sunlight was called the photodynamic effect. In 1903, using the example of PDT treatment of skin cancer using eosin as FS, it was proved that the accumulation of eosin in cells with proliferative activity occurs more intensively than in healthy cells. In Russia, PDT has been used since 1992 in the treatment of malignant tumors of the skin and internal organs, as well as some non-tumor diseases: purulent wounds, trophic ulcers, psoriasis, and prevention of opacity of the transplanted cornea [5]. According to foreign sources, there are isolated cases of successful use of PDT in the treatment of dysplasia and cervical cancer [4,7,8,9,10].

The necessary components for PDT are laser light sources and photosensitizers (FS). Typically, PDT uses laser light sources with a high radiation power density in the required range, the ability to deliver light using fiber optics without significant power loss, the ability to measure the radiation dose. Dye lasers or semiconductor lasers with an output power of up to 5 W [1,2]. Are most often used for PDT. The second important component of PDT is FS, a substance that increases the sensitivity of biological objects to light. The following groups of FS are known: hematoporphyrin derivatives (Photohem, Photosan, Photofrin), sulfated aluminum phthalocyanine (Photosens) [11,12]. A new stage in the development of PDT was the use of chlorin E6 derivatives (Photoditazine), which have higher photodynamic activity and improved pharmacokinetic properties [2, 12]. Until recently, there was only an intravascular method of administration of FS, however, based on experimental studies indicating the manifestation of a photodynamic effect with local use of FS, for the first time a FS for topical use was developed - "Photoditazine" in the form of a gel. For the success of PDT, the time during which the ratio of the dye concentration in pathological and healthy tissue reaches a maximum is important. In derivatives of hematoporphyrin and sulfonated aluminum phthalocyanine, the peak of the maximum concentration ratio occurs after 24 - 48 hours, in derivatives of chloride E6 it is reduced to 2 hours [1]. The necessary properties of FS that ensure the effectiveness of PDT are: selective absorption by pathological tissue, sufficient penetration into the cell, the ability to generate a high quantum yield of singlent oxygen, rapid excretion from the body [13,14,15,16]. The main parameters of PDT are the dose of FS, the radiation dose and the time interval between the introduction of FS and the irradiation of pathological tissue [3,5]. Of great importance for PDT is also the radiation power density, which is the ratio of the radiation power at the output of the light guide P (W) to the area of the irradiation field S (cm) [1,5]. PDT is carried out as follows: FS is injected intravenously or applied to the pathological zone, after a certain time required to achieve the difference in the concentration of the drug in the pathological and normal tissue, the lesion is irradiated with light, the wavelength of which corresponds to the peak absorption of the injected FS [5]. The result of the action of FS and light is the death of pathological cells. Selective damage to pathological cells is ensured by the selectivity of FS accumulation in pathological tissue and local irradiation of pathological tissue. The mechanism of selective accumulation of FS has not been definitively studied. However, there are a number of factors contributing to the selective accumulation of FS in pathological tissue: * In the blood, FS binds to serum blood proteins: lipoproteins, albumins, globulins. The longest binding of PS (more than 48 hours) is observed with lipoproteins (liposomes). Since cells with increased proliferative activity contain a large number of lipoprotein receptors that capture lipoprotein complexes with PS, this determines the selectivity of their accumulation. * The selectivity of FS accumulation is ensured due to a lower pH in pathological tissue compared to normal tissue. With a decrease in pH, FS dissolve better in aqueous solutions, which contributes to a more pronounced saturation of pathological tissue with them. * The selectivity of FS accumulation in pathological tissue is also due to changes in the vascular system, which manifest themselves in the form of an incomplete basement membrane and increased permeability of the endothelium [11,12,13,15]. The damaging effect of PDT is realized through photooxidation reactions. There are two main ways of reaction of excited FS. Type I photooxidation involves a direct reaction of the excited FS with the substrate due to the mechanism of hydrogen involvement or electron transfer, which leads to transition radicals, which then react with oxygen. In type II reactions, energy transfer occurs from the excited triplet state of the sensitizer to

molecular oxygen and singlent oxygen is formed, which then reacts with substrates amenable to oxidation. As a result, photo destruction of biologically important molecules develops: nucleic acids, proteins, phospholipids [1,2]. Under the action of PDT, the cytoplasmic membrane, the membranes of the nucleus and nucleoli, mitochondria, lysosomes, Golgi apparatus, endoplasmic reticulum are damaged [11,12]. In addition to direct photochemical effects on cells with proliferative activity in PDT, an important role in the mechanism of destruction is played by a violation of the blood supply to pathological tissue due to damage to the vascular endothelium and hyperthermic effect [1,5]. A few hours after PDT, there is a cessation of normal cell movement and the formation of many bubbles on the membrane. Bubbles, which are often the same size as the cell itself and the structure of the "balloon" protruding from the membrane, mean serious damage to the membrane. After the formation of bubbles, there is no cell division and lysis occurs [3]. The maximum light absorption of biological tissues is in the region of 610-800 nm, so red light penetrates well through the skin and mucous membranes. Approximately in the same zone (662nm) there is a long-wave absorption band of FS - derivatives of Eb chloride . The absorption of red light by tissues occurs at a depth of 1-1.5 cm [11]. Side effects of PDT include: photo sensitivity of the skin, depending on the choice of FS and dictating the need to comply with a limited light regime. According to A.F. Tsyb (2002), the frequency of photo toxicity when using Photohem is 31.3%, Photosense - up to 80%. The data published in the foreign literature available to us on the use of PDT in the treatment of cervical diseases are based on a small number of observations. There are no clear indications and contraindications to PDT, there is no consensus on the required dose of laser radiation, methods have not been developed using a new generation of Photoditazine FS.

Thus, the analysis of literature data confirmed that the choice of treatment method depends on the size and nature of changes in the cervical mucosa, the location of the "transition zone" (as a high-risk zone) in relation to the external pharynx. When choosing a treatment method, the age of the woman, the combination of cervical diseases with concomitant gynecological and extra genital pathology is important. When analyzing the literature, there are differences both in the methods of examination and in the differentiated approach to the choice of treatment method. In many clinics to date, the main method of treating cervical pathology is diathermocoagulation and diathermoconidation. The widespread use of this method in our country is explained by the ease of implementation and cost-effectiveness. A lot of side effects observed after the electrosurgical method exclude its use in women who have not given birth. Pregnant women with diathermocoagulation and a history of many researchers recommend that they be allocated to a special risk group. Many authors consider laser imaging and radiosurgery to be the most promising in terms of effectiveness and absence of complications in the treatment of background and precancerous diseases. However, the high cost of the equipment limits the use of these methods in practical healthcare. The analysis of modern data shows that there is no "ideal" method of treatment, therefore, the research and introduction of new technologies in the treatment of pathological conditions of the cervix into practical healthcare is very relevant. The presented literature data allow us to conclude that the search for rational methods of treating cervical diseases is a promising task, not only in terms of preventing cervical cancer, but also preserving the structural and functional characteristics of the cervix as the most important factor in the reproductive health of the female body. Photodynamic therapy presents great opportunities in this regard.

Modern tactics of treatment of cervical diseases

Numerous studies have been devoted to the problem of the treatment of background and precancerous diseases of the cervix, the results of which indicate either the advantages or insufficient effectiveness of the methods used. According to most authors, when choosing a treatment method, two basic principles must be observed: firstly, the method should provide a reliable cure to prevent relapses and the transition of the disease into a more pronounced pathological process; secondly, if possible, use organ-preserving and sparing interventions, especially in young women [1,2,3,5]. Generally recognized methods of treating cervical pathology are effects aimed at destroying the surface pathologically altered epithelium with subsequent normal epithelialization of the vaginal part of the cervix. According to the literature, the most common methods are based on the use of diathermocoagulation methods, quantum radiation energy (lasers) and low temperatures

(cryodestruction) as a therapeutic effect. According to domestic and foreign authors, the therapeutic effect of their use is 87- 96,2 % [11,12]. Previously used agents that improve regeneration (sea buckthorn oil, methyluracil, vitamin A) contribute to the strengthening of proliferative processes, and agents with coagulation properties (vagotyl, trichloroacetic acid) affect only the surface layer of the epithelium, which contributes to the occurrence of relapses [5]. Given the low effectiveness, these methods of treatment have been practically not used recently. Currently, the drug "Solkovagin", which is a mixture of organic acids, is used from coagulating agents.

However, indications for the use of this drug are very limited [1,5] because there is no control of the depth of exposure. Application experience of V.N.Prilepskaya et al. (2015) Solkovagina indicates low efficacy in leukoplakia, as well as the impossibility of use in the presence of an atypical picture. Currently, the most common methods of treating cervical diseases are physical methods of destruction: diathermocoagulation, cryodestruction, laser vaporization. Diathermocoagulation has been used in our country since 1935, and until recently, it was the most common method of treatment. The influence factor of diathermocoagulation is the heat generated by the passage of current through the tissue. For the purpose of diathermocoagulation, universal devices for surgical diathermy are used with the possibility of monoactive and bioactive coagulation methods. The method of diathermocoagulation is based on the fact that electric currents cause tissues to warm up near the active electrode to 80-200 ° C, the frequency of the current used is up to 2 MHz at a current strength of 0.7 to 2 amperes and a voltage of 3 to 10 volts. This method has a number of complications associated with the damaging effect of electric current on the underlying tissues. The previously used mono-active method of diathermocoagulation gives significant coagulation both on the surface and in the depth of tissues. When using the bipolar mono-active coagulation method, it is possible to warm up tissues and fluids located between the active and passive electrode to 60-100° C. which may be accompanied by irreversible coagulation of protein structures. Clinically, such complications are manifested by postoperative cystitis, parametritis, thrombophlebitis of the lower extremities and pelvis, erosive lesions of the rectum, symptoms caused by damage to the spinal cord roots. A milder mode of exposure is observed with biactive diathermy, which is widely used at present. However, even in this case, a deep and uneven effect of electric current on the fabric is characteristic. With the pathology of the endocervix, using this method, a cone-shaped excision of the mucous membrane of the cervical canal and the surrounding tissue is possible using an electric loop (diathermoconidation). However, even in this case, a deep and uneven effect of electric current on the fabric is characteristic. According to foreign researchers, the indication for diathermoconidation is cancer in situ, CIN I, CIN II [1,2].

However, domestic and some foreign scientists use diathermoconisation for ectropion and cervical deformity [5]. According to Ya. V. Bokhman (1989), diathermoconidation can contribute to the progress of a previously undiagnosed malignant process.

In the studies of Ya.V. Bokhman (1989), 8% of patients with cervical cancer had a history of diathermoconidation. Complications arising after the use of diathermoconidation, according to researchers, are similar to those after diathermocoagulation due to a single mechanism of action on tissues. Complete morphological restoration of the cervix according to V.I. Bychkov and co-authors (2011) after diathermocoagulation occurs in terms of 9 to 12 months. Tissue destruction is noted not only in the epithelium, but also in all structures of the cervix - muscles, vessels, and the inervation apparatus, which is accompanied by a number of undesirable effects: the occurrence of bleeding during scab rejection (1.5 - 15%), the occurrence of endometriosis of the cervix (24 - 55%), violation of the architectonics of the cervical canal (40%), especially after diathermoconization, up to its overgrowth, violation of reproductive function (3 - 24%) [11,15]. So, M.N. Kostava (2017) and V.N. Prilepskaya (2015) in 3% of patients who underwent diathermocoagulation, infertility was revealed, which was explained by a violation of the anatomical functional integrity of the cervix; in 24%, spontaneous miscarriages were registered against the background of isthmic - cervical insufficiency that frolicked after diathermocoagulation; in 4.7%, cervical dystocia in childbirth. Clinicians clearly consider it appropriate to single out patients who have undergone diathermotherapy in the risk group for birth trauma [11]. In addition, according to the authors, after diathermocoagulation, exacerbations of inflammation of the uterine appendages, menstrual cycle disorders, pain syndrome often occur. The frequency of relapses when using diathermocoagulation is 9 - 55% [12,15]. Diathermocoagulation of recurrent diseases of the cervix, according to a number of authors [1], in most cases are ineffective,

leads to structural disorders, dyskeratosis, the occurrence of leukoplakia, which is due to a violation of the trophic tissues.

Thus, it follows from the literature data that a lot of experience has been accumulated in the study of complications of diathermocoagulation, indicating the significant traumatism of this method and the risk of developing a large number of complications. Therefore, the use of diathermocoagulation can be considered inappropriate for the treatment of benign diseases of the cervix. However, the analysis of literature data has shown the popularity of diathermoconisation in cervical deformity, pre-cancer and initial cervical cancer. Significant success in the treatment of benign cervical diseases has been achieved due to the introduction of cryodestruction [1,2,3,5]. The cryodestruction method is based on the crystallization of water in tissues with the formation of growing extracellular and intracellular crystals that destroy cellular structures, the concentration of electrolytes, denaturation of biomolecules, biological membranes, lipid - protein complexes, microcirculation disorders and ischemia [1,5]. In cryotherapy, nitrogen or nitrous oxide is used as refrigerants. Cryotherapy does not require stationary conditions, because it is painless and practically safe. Cervical epithelialization occurs faster than with diathermocoagulation, which is due to limited necrosis and significantly less damage to the surrounding underlying tissues. According to T.A. Fokina and V.N. Prilepskaya (2013), unlike diathermocoagulation, cryotherapy does not cause sclerosis of connective tissue, does not deform the cervix, does not adversely affect the processes of cervical dilation during childbirth. Cryodestruction is recommended for the treatment of exocervix transformation zone, ectopia, endometriosis, leukoplakia, grade I - II dysplasia [11,15]. However, there is an opinion [1,2] that cryotherapy is not always effective for leukoplakia, endometriosis, scarring and ectropion of the cervix. The disadvantages of the method are: the impossibility of local removal of the pathological site with minimal traumatization of the underlying tissues, insufficient depth of exposure, a relatively high frequency of recurrence of cervical diseases after therapy is observed from 15 to 40%, the inability to use cryodestruction in the treatment of scarring of the cervix, abundant liquid discharge that lasts for several days, a large loss of ions potassium [11,15]. The literature data confirmed that cryosurgery is widely used in the clinical practice of gynecologists. However, the evaluation of the effectiveness, indications and contraindications to this method are ambiguously defined. In recent years, laser radiation has become very popular in the treatment of cervical pathology [1,2]. In gynecology, the following types of surgical lasers are most widely used: carbon dioxide laser (COg laser), aluminum-yttrium garnet laser with neodymium (Nd-YAG laser), holmium (NoYaG), argon laser. According to domestic and foreign researchers, the mechanism of action of high-energy (surgical) lasers is the conversion of laser radiation energy into thermal. As a result of absorption of laser radiation by tissues, they are instantly heated to high temperatures. This leads to rapid and intense evaporation of interstitial and intracellular fluid, coagulation or evaporation of cellular structures and the formation of a zone of coagulation necrosis at the border with surrounding tissues [1,5]. Depending on the degree of heating, the effect of the laser is manifested in the effects of incision or surface evaporation of tissues. The incision of the tissue is carried out by focused laser radiation due to layer-by-layer evaporation on an ultra-small area. The volumetric power density reaches several hundred kilowatts per 1 cm3 , the spot diameter is not more than 1 mm . Layer-by-layer evaporation (vaporization) is produced by a beam of lower energy. The volumetric power in this case is 5-7 kW / cm, the spot diameter is up to 2-3 mm or more [5]. The advantages of laser therapy include minor tissue injury, absence of cervical canal stenosis, sterilizing effect of laser radiation, relatively rare cases of bleeding, control of the depth of exposure, the possibility of capturing large lesions, minimal traumatization of surrounding tissues [1,3]. Healing of "laser" wounds, according to V.M. Zuev (2008), G.K. Chew et al. (2019), occurs rapidly due to a decrease in leukocyte infiltration that occurs during the formation of a laser tissue defect, a reduction in the phases of exudation and proliferation. Regeneration under laser exposure begins on 8-10 days, ends after 4-6 weeks. Taking into account all the advantages of laser treatment, A.M. Zuev (2008), V.N. Prilepskaya et al. (2012), G. Stellato et J.Paavonen (2015) believe that indications for its use may be benign neoplasms of the cervix, dysplasia of the I-III degree, carcinoma in situ. The efficiency of the method is 86 - 98.7%, and when combined with the action of a helium-neon laser, it reaches 100% [1,2,3,5]. However, a number of scientists [1] noted that when removing extensive ectopias with pronounced proliferation of the glandular epithelium, laser exposure may be accompanied by increased bleeding. Bleeding, according to the authors, can also occur when tissues evaporate to a depth of more than 3 mm. Therefore, in such cases, they recommend taking precautions and preventive measures (increasing the diameter of the laser spot to 7 mm or more, bringing a hemostatic sponge to the cervix, limiting physical activity, sexual rest). With arterial bleeding, suturing is indicated. With an extensive process spreading from the cervix to the vagina, the authors recommend two-stage treatment.

Thus, the literature data of recent years have demonstrated the high efficiency of laser treatment for various diseases of the cervix. However, along with the great advantages of the laser, its use is limited due to expensive equipment and the need for engineering maintenance. Laser technology also requires special training of medical personnel. The use of these destructive methods of treatment of cervical diseases is not justified in the presence of scarring [16,18,20]. The long-term existence of old ruptures leads to the development of a chronic inflammatory process, which in turn can cause pathological changes in the mucous membrane of the cervix. The necessary conditions for the full treatment of cervical diseases in combination with scar deformation is the elimination of deformation.

Currently, various methods of plastic surgery are known."surgery with a combination of pathological changes with deformity of the cervix: Emmett surgery, wedge-shaped amputation by Schroeder, cone-shaped amputation by Sturmdorf. However, the listed operations, according to the majority of authors [1]. Violate the anatomical and functional features of the cervix due to its shortening and changing the shape of the cervical canal. At the same time, the architectonics of the cervix is violated, the mucous plug is not retained in the cervical canal, increasing the risk of chronic inflammatory diseases. The need to preserve the anatomical and functional usefulness of the cervix, which is especially important in patients of reproductive age planning childbirth, has led to the development and introduction into operative gynecology of more sparing surgical methods, such as reconstructive plastic surgery [5,22]. The essence of the operation is the splitting of cervical tissues into internal and external flaps with subsequent excision of scar — altered tissues, formation of the cervical canal and external pharynx. This technique, according to the authors, promotes better tissue healing and makes the operation effective, restores the normal anatomy of the cervix and the fusiform shape of the cervical canal [20]. In order to improve the results of reconstructive plastic surgery by the method of dissection, the use of preserved dura mater tissue and hydrogel with prolonged release of antiseptic and antibiotic for the prevention of postoperative infectious complications has recently been proposed [17,19,21].

Thus, the high efficiency of the surgical method for pathological changes of the cervix against the background of its deformation makes it the method of choice for the treatment of these nosological forms of cervical pathology. A relatively new method of treating cervical diseases is a kind of electrosurgical method - radio wave surgery. The principle of radio wave exposure consists in using the output frequency of the current in the range of 3.8 MHz, which distinguishes it from previously used electrosurgical devices with an output frequency of no more than 1.76 MHz. Unlike the electrosurgical method, the principle of operation of the radio wave is not to coagulate the tissue, but to evaporate it by disrupting the stability of the intrinsic electromagnetic fields of the molecules that make up the tissue. A number of authors [16] high atraumatic, significant ease of tissue dissection and good hemostasis, absence of rough scab. Wound healing after radiosurgical exposure occurs under a fibrin film, which is rejected for 8-14 days. Complete epithelialization of the wound is noted after 28-40 days. Unlike diathermocoagulation after radiosurgery, bleeding is extremely rare. This method is successfully used in the treatment of background and precancerous diseases of the cervix. The effectiveness of the radio wave method is 94,1 - 98,7% [1,2,3,5].

After analyzing the long-term results of treatment of benign cervical diseases by radiosurgical method, the researchers noted the almost complete absence of relapses. It should be noted that this method of treatment has been used relatively recently in our country and the experience of application in gynecology is insignificant.

Conclusions

1. The important role of the cervix in the reproductive system of women is due to its structural and functional features, which largely determine the possibility of full-fledged fertilization, uncomplicated pregnancy and timely delivery. Patients who had an unfavorable pregnancy outcome in the anamnesis, who are at risk, need an individual approach.

2. This is especially true for patients with cervical diseases during pregnancy planning. Given the large number of studies devoted to the pre-pregnancy preparation of patients with pregnancy loss, no algorithm has been developed for the examination and management of patients with cervical diseases.

3. At the same time, there are practically no studies on the peculiarities of the management of patients with cervical diseases and tactics at the stage of pregnancy planning.

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Entered 09.08.2022