ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ
Өсімдіктердің биологиясы және биотехнологиясы институтының

Х А Б А Р Л А Р Ы

ИЗВЕСТИЯ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН
Института биологии и биотехнологии растений

N E W S

OF THE NATIONAL ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN
of the Institute of Plant Biology and Biotechnology

SERIES
OF BIOLOGICAL AND MEDICAL

4 (334)

JULY – AUGUST 2019

PUBLISHED SINCE JANUARY 1963

PUBLISHED 6 TIMES A YEAR

ALMATY, NAS RK

«ҚР ҰҒА Хабарлары. Биология және медициналық сериясы».
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Меншіктенуші: «Қазақстан Республикасының Ұлттық ғылым академиясы» РҚБ (Алматы қ.)
Қазақстан республикасының Мәдениет пен ақпарат министрлігінің Ақпарат және мұрағат комитетінде 01.06.2006 ж. берілген **№5546-Ж** мерзімдік басылым тіркеуіне қойылу туралы куәлік

Мерзімділігі: жылына 6 рет.
Тиражы: 300 дана.

Редакцияның мекенжайы: 050010, Алматы қ., Шевченко көш., 28, 219 бөл., 220, тел.: 272-13-19, 272-13-18, http://biological-medical.kz/index.php/en/

Типографияның мекенжайы: «Аруна» ЖК, Алматы қ., Муратбаева көш., 75.

«Известия НАН РК. Серия биологическая и медицинская».
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Собственник: РОО «Национальная академия наук Республики Казахстан» (г. Алматы)
Свидетельство о постановке на учет периодического печатного издания в Комитете информации и архивов Министерства культуры и информации Республики Казахстан **№5546-Ж**, выданное 01.06.2006 г.

Периодичность: 6 раз в год
Тираж: 300 экземпляров

Адрес редакции: 050010, г. Алматы, ул. Шевченко, 28, ком. 219, 220, тел. 272-13-19, 272-13-18,
www:nauka-nanrk.kz / biological-medical.kz

Адрес типографии: ИП «Аруна», г. Алматы, ул. Муратбаева, 75

News of the National Academy of Sciences of the Republic of Kazakhstan. Series of biology and medicine.
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Owner: RPA "National Academy of Sciences of the Republic of Kazakhstan" (Almaty)
The certificate of registration of a periodic printed publication in the Committee of information and archives of the Ministry of culture and information of the Republic of Kazakhstan N 5546-Ж, issued 01.06.2006

Periodicity: 6 times a year
Circulation: 300 copies

Editorial address: 28, Shevchenko str., of. 219, 220, Almaty, 050010, tel. 272-13-19, 272-13-18,
http://nauka-nanrk.kz / biological-medical.kz

Address of printing house: ST "Aruna", 75, Muratbayev str, Almaty

N E W S
OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN
SERIES OF BIOLOGICAL AND MEDICAL
ISSN 2224-5308
Volume 4, Number 334 (2019), 5 – 11 **https://doi.org/10.32014/2019.2519-1629.33**

UDS 76.29.49
DOL 616-002.3-08:615.831

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PHOTODYNAMIC THERAPY IN THE TREATMENT OF PATIENTS WITH PURULENT WOUNDS

Abstract. Nowadays, a relatively new medical technology, photodynamic therapy, is being actively developed and introduced into clinical practice. The method is based on the ability of many biological objects (tumor, microbial cells) to accumulate chemicals - photosensitizers, after which they become sensitive to sunlight, as well as to laser radiation of a certain wavelength. In cells that have absorbed a photosensitizer, a photochemical process is launched with the generation of singlet forms of oxygen, which has a destructive effect on biological systems. The review presents information on the use of photodynamic therapy, based on the integrated use of light and chemical compounds - photosensitizers, which is one of the areas of laser medicine. The relevance of the review of the existing capabilities of PDT is due to the great interest of surgeons in the use of this method in the treatment of purulent wounds. The article provides a brief historical background on the development of this method of treatment, covers the principles and mechanisms of its action. The possibilities of using photodynamic therapy in surgical practice are analyzed. The prospects of further development of the method for the treatment of purulent-necrotic wounds are substantiated.

Key words: laser medicine, photodynamic therapy, photosensitizer, purulent wound.

The treatment of purulent wounds of various etiologies is an urgent problem of surgery up to the present time and has a tendency to grow, has a long history [1]. One of the principles of treatment of purulent wounds of various origins is the use of antibacterial drugs of various groups that cannot guarantee reliable prevention of infectious complications, due to the rapid adaptation of wound microflora, as a result of which the formation of antibiotic-resistant microorganisms occurs. It is necessary to take into account the decrease in the immunological response of the body after the use of drugs in this group, a violation of intestinal flora [1-3]. Despite the success of surgery over the past decades, it should be noted that the frequency of purulent complications remains almost unchanged. For a long time, mankind has been searching for methods of treating wound infections, there have been promising achievements - this is largely due to the discovery and the beginning of the use of antibacterial agents in the first half of the 20th century, and subsequently with the use of proteolytic enzymes. However, these methods did not have a universal effect on the wound process, needing further development [1, 2]. To date, the principle of treatment of purulent wounds involves a wide disclosure of the suppurative focus, followed by open wound management [1-3]. The disadvantages inherent in this method are the impossibility of carrying out a frequent change of gauze dressings during the day, damage to the forming granulation tissue when changing the dressing [3]. This creates prerequisites for increasing the duration of treatment, creating economic losses for the patient and for the state due to the long disability time. The most important condition for the local treatment of wounds in the postoperative period is drainage, the task of which is to remove wound exudates and products of wound exudates, the application of modern wound coatings, such as sorption, protective, containing drugs, atraumatic is also important [3]. Treatment of purulent wounds should be complex, taking into account the clinical manifestations of the disease of a single patient, the presence of background pathology, indications and contraindications for the appointment of surgical and medical treatment [3].

Photodynamic therapy (PDT) seems to be a promising method in the treatment of purulent wounds as part of complex treatment, which uses a combination of low-frequency laser radiation with a wavelength of 630 - 1300 nm in combination with photosensitizers, leading to the development of a photochemical reaction in the presence of interstitial oxygen, which has a destructive effect on intracellular structures [4]. PDT is a relatively new trend in the treatment of purulent wounds; by now, sufficient clinical experience has been gained in using this technology, which is reflected in many papers [5, 15]. The launch of a photodynamic reaction is possible in the presence of a special chemical - a photosensitizer and light. The main active substrate is the photosensitizer, the latter is absorbed by the target cell, the inactive photosensitizer is inert and has no effect [6]. Absorbed quantum of light of a certain wavelength can lead to the activation of a substance molecule [5, 18]. The light source must have the necessary power, which will allow to deliver the radiation energy to the target cell and the molecular oxygen present in it, which is in a stable state and is characterized by the lowest level of molecular energy [5, 22]. Under the action of a photosensitizer in the presence of light, the oxygen molecule passes into a singlet form, which has a high chemical activity, with subsequent damage to the cell structures. Damage to biological structures, necrotic and apoptotic changes are the result of the launch of free radical reactions. The oxidation of biologically important molecules under the influence of visible light in the presence of molecular oxygen and a photosensitizer is called the photodynamic effect [5].

Currently, PDT is actively used in many countries and has such advantages as low invasiveness, selectivity of effects on the pathological focus, the ability to repeat courses of PDT, low systemic toxicity. [7-10]. The method has advantages over antimicrobial treatment, since the effectiveness of PDT is not related to the spectrum of sensitivity of microorganisms to antibiotics, it is successful even in the treatment of antibiotic-resistant strains of Staphylococcus aureus, Escherichia coli and other microorganisms that do not develop resistance to PDT, unlike exposure to antibiotics. Tissue damage in PDT is local, the bactericidal effect is limited to the area of laser irradiation of photosensitized tissue, thus avoiding the side effect that occurs when using antibacterial drugs for the treatment of surgical infection with local PDT. The method has found widespread clinical application in oncology, due to the selective accumulation of the photosensitizer in tumor tissue. Activation of the drug occurs when a local light exposure to the wavelength corresponding to the maximum absorption, leading to the generation of singlet oxygen, which leads to damage to the intracellular structures of the tumor cell [12, 14, 17, 20].

Nowadays PDT has found extensive use in many fields of medicine, the method is used to treat tumors of the skin, breast, lungs, bladder, infectious diseases, certain diseases of the skin and eyes, ENT organs, oral cavity. The effectiveness of such treatment is high with minimal load on the body [11, 13, 22, 23].

To date, there are more than 400 substances that have a photosensitizing effect. Derivatives of hematoporphyrin, chlorine, 5-aminolevulenic acid, phthalocyanine are most common in the manufacture of medical drugs [16, 18, 19, 26].

The use of photochemical reaction energy for treatment has been known for over 6000 years, when light-sensitive substances of some plants were used to treat skin diseases, in particular, for the treatment of vitiligo, a powder of dried parsley leaves, St. John's wort, parsnip was used, which was applied to depigmented areas of the skin and insolated with sunlight before the appearance of pigmentation by the type of tan [5, 21]. For the treatment of the same pathology, Ammimajus plant powder (large Ammi or Chinese cumin) was later used, the phototherapeutic effect was due to the content of photocoumarins, which have a pronounced phototherapeutic effect, and in the twentieth century, Ammimajus was used to synthesize the medical drug Ammifurin, used to treat vitiligo, psoriasis, lichen planus, neurodermatitis [18, 21].

O. Raab discovered the photochemical oxygen-dependent reaction for the first time in 1897. As a student at the University of Munich Pharmacological Institute, he studied the effects of dyes on paramecium microorganisms (Paramecium) [21, 28, 32, 33]. He noticed that these microorganisms that are in a solution of acridine orange die when they hit the light, but when they are in the dark they can move freely [21, 26, 28]. Further studies conducted under the guidance of Professor H. Tappeiner suggested that fluorescent substrates like acridine dye transform light energy into an active chemical reaction that leads to the death of microorganisms [21, 29, 31]. Based on the results of a study by H. Tappeiner and X. Jesionek, in 1903, the first PDT session was performed for a patient with skin cancer, using eosin as a photosensitizer [34]. In 1905, they described the results of treatment of 6 patients with basal cell carcinoma of the face skin by local application of 1% eosin solution and prolonged exposure to sunlight or artificial radiation of an arc lamp [21, 30]. They managed to achieve complete resorption of foci in 4 patients with a duration of 1 year without a recurrent period. At the same time, H.Tappeiner and A. Jodlbauer coined the term "photodynamic action" [35]. In 1908 W.H. Hausmann makes a report on the phototoxicity of hematoporphyrin and concludes that hematoporphyrin is an active sensitizer for paramecium and red blood cells [36].

For the first time in 1912 F. Meyer-Betz experimentally demonstrated the effect of hematoporphyrin on the human body on itself [37]. After intravenous administration of 0.2 g of hematoporphyrin, solar photosensitivity is observed, manifested as edema and hyperpigmentation, lasting up to 2 months [21, 37].

The development of photodynamic therapy was promoted by the discovery of a new photosensitizer, hematoporphyrin, which showed higher efficiency compared to previous analogues. After some time, a derivative of hematoporphyrin (HGP, Hematoporpherinederivate - HpD) was synthesized, which turned out to be 2 times more effective than the original compound, but its toxicity declined higher [5, 38]. This drug was obtained by S. Schwartz by acting hematoporphyrin with concentrated solutions of sulfuric and acetic acids, HpD was used in the USA in 1960 for the diagnosis of neoplastic diseases [39].

The use of lasers in medical practice contributed to the further development of the method (the first half of the 1960s), since the laser was monochromatic, using the most optimal wavelength for a particular photosensitizer, leading to a higher intensity of the photochemical reaction [26], it also became possible to transfer the light flux through fiber-optic systems with targeted impact on the organs and tissues of the body containing a photosensitizer, which certainly led to the intensive use of the method in various fields of clinical practice [5, 26].

In PDT with photosensitizers of the first generation, positive results were obtained in the treatment of patients with purulent wounds, acceleration of wound cleansing from purulent necrotic detritus, stimulation of tissue regeneration processes was noted. At the same time, the use of photochemical preparations of the first generation was also marked by significant shortcomings, such as a long half-life from the body, often enough allergic reactions and a significant increase in the photosensitivity of the whole body for a long period of time [23].

The drug Photofrin II is used most often today, it is called the "workhorse" of PDT [21], cumulated in all tissues and organs of the reticuloendothelial system [16]. The longer delay of Photofrin II is noted in the tumor tissue, however, the prolonged delay in the skin cells (even at minimum concentration) of the photosensitizer dictates the need to limit the light regimen by patients for 4-6 weeks, to prevent skin burn like sunburn [5, 10, 21]. In Russia, the analogue of Photofrin II is a drug Photogem, synthesized under the guidance of Professor A.F. Mironov in 1990. Photohem is fluorescent in the red region of the spectrum, which also allows it to be used to verify the tumor process of determining its boundaries [5, 7, 21].

In the mid-1990s, clinical trials of a second-generation photosensitizer, Photosens, began in Russia. The drug has an intense absorption band in the red region of the spectrum 665-675 nm. High photochemical activity in the red region of the spectrum, higher transparency of the tissue for laser radiation, which allows to affect deeper tissues are the advantages of second-generation photosensitizers over the first, since the main limitation of the PDT method is the depth of penetration of laser radiation into the tissue [5, 21]. From the point of view of the methodology, the development of algorithms for the individual selection of parameters of light exposure in PDT seems promising. For example, of great interest is the possibility of selecting the density and dose rate of laser irradiation based on the data of fluorescent diagnostics [40].

The parameters to which the optimal photosensitizer must correspond, including biological, photophysical and chemical-technological criteria, were determined as a result of years of research. They are low toxicity, high elimination, high absorption in the spectral range, high selectivity of drug absorption by tumor cells [5, 7, 20]. The creation and introduction of photosensitizers with the ability to accumulate at a high rate in the tumor tissue and to quickly decay is of particular interest [5, 24]. One of the most significant factors limiting the possibilities of the method is the depth of penetration of the laser flux [5, 7].

Contraindications to laser PDT are the presence of malignant neoplasms, decompensation of cardiovascular activity, acute impairment of the cerebral circulation, hepatic and renal failure [41].

In the study of professors A.V. Geinitz, P.I. Tolstykh, V.A. Derbenyov et al. demonstrate a positive clinical effect of PDT in 80 patients with purulent wounds of soft tissues, the majority of patients were operated on with phlegmon and abscesses of various localization. The application of gel "Photoditazine" 0.1% on the wound was carried out, the exposure of the drug on the wound was not less than 2 hours. When exposed to PDT, researchers recorded an acceleration in the rate of wound cleansing from necrotic masses (within 2-3 days), allergic reaction to the photosensitizer was not registered. Evaluation of the results of treatment of patients with nonhealing wounds shows faster cleansing of the wound from necrotic masses, early appearance of granulation and marginal epithelization in patients of the main group, which was carried out photodynamic therapy, a decrease in the microbial contamination of wounds was recorded, this is due to the high level of accumulation of exogenous photosensitizer by microbial cells, and their own cells located in the area of the wound defect accumulate photosensitizer in a much smaller volume compared to bacteria. When studying local microcirculation, a decrease in edema in the area of a nonhealing wound, improvement of blood flow in the capillary bed, formation of a microcirculatory network, reduction of vascular resistance were noted. The expressed bactericidal effect of PDT on the basis of cytological data, rapid wound cleansing (3-5 days for the first or second session of photochemotherapy) was shown. Activation of the macrophage reaction leads to the stimulation of the wound process. After 1-2 weeks, the number of macrophages in the tissue increases significantly, mature macrophages with active phagocytic function prevail. In the main group, a more rapid transition of the wound process from the inflammatory to the reparative phase, maturation by the end of the second week of full-fledged granulation tissue, the transformation of the latter by the end of the third week into fibro-cicatricial, epidermis regeneration takes place, the wound size decreases due to epithelialization and contraction of the scar tissue. PDT in the treatment of nonhealing wounds contributes to the acceleration of the torpid wound process consistently leading to a reduction in the time of all phases of wound or ulcer healing. The method developed by the authors showed high efficacy compared with traditional treatment, allows to reduce the time of epithelialization of the wound 1.7 times while providing a good functional and cosmetic effect [25].

The advantages of antibacterial PDT include the same efficacy in acute and chronic infection, the method is also effective against bacteria, protozoa, fungi and viruses, photosensitizer does not have toxic and mutagenic effects; PDT does not depend on the spectrum of sensitivity of microorganisms to antibiotics; PDT's bactericidal effect is local, limited to the laser irradiation zone of sensitized tissues, which avoids microflora damage typical for antibiotics in areas not subject to irradiation, the possibility of repeated courses of treatment and combination in one diagnostic and treatment procedure [26, 27]. An additional advantage of PDT is its relative painlessness and the possibility of repetition in an outpatient basis.

As for the efficacy of PDT in patients with purulent-necrotic wounds, V.S. Panteleev in his study [42], demonstrated the effectiveness of skin graft engraftment by photodynamic effect “Photoditazine” in combination with laser antibiotic therapy. The authors provide information that as a result of the treatment, namely: patients with purulent necrotic wounds in the first study group, the removal of necrotic masses were removed using a low-frequency ultrasonic cavitator "SONOCA – 180" (Germany). In the second main group necrectomy was performed using carbon dioxide surgical laser "Lancet" (Russia), the third group was the control group. After the necrectomy stage, all patients of both main groups were subjected to a photodynamic effect with the second generation of photosensitizer “Photoditazine” in the form of 0.5% penetrator gel at the rate of 1 ml of gel per 45 cm^2 of the irradiated surface. After 2 hours from the moment of applying the FS, laser irradiation of the wound was performed using the Atkus-2 laser apparatus (Russia) in continuous mode with a power density of 1 W/cm^2 and a wavelength of 661 nm. In both major groups, antibiotics were activated by intravenous laser irradiation of blood (ILBL). As a result of the technique, the authors managed to reduce the time of preparing the wound surface for autodermoplasty by an average of 3 days, reduce antibiotic therapy by 1.3 times, and improve the effectiveness of skin graft engraftment by 24%.

Prof. Tolstykh P. I., Derbenev V. A. et al. [43] demonstrate the results of treatment of 129 patients with purulent wounds of different localization on the background of the use of a photosensitizer of the chlorin series (photoditazine) in patients of the main group, the reduction of the time required for cleansing wounds and the earlier beginning of epithelialization in patients of the main group was shown on the background of a more rapid decrease in bacterial contamination of the wound. A morphological study proved more rapid relief of inflammation, reduction of microcirculatory disorders, increased phagocytic activity of neutrophils, accelerated maturation of granulation tissue during photodynamic therapy, and an elastic scar was formed in the main group of patients in a shorter time.

As a result of the research, the list of diseases, including surgical profile, for the treatment of which photodynamic therapy can be used, is constantly expanding. The possibilities of using this method are constantly expanding and photodynamic therapy is an alternative to the already existing methods and approaches in the treatment of purulent surgical diseases.

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ІРІҢДІ ЖАРАМЕН ПАЦИЕНТТЕРДІ ЕМДЕУ КЕЗІНДЕГІ ФОТОДИНАМИКАЛЫҚ ТЕРАПИЯ

Аннотация. Қазіргі уақытта жаңа медициналық технология – фотодинамикалық терапия клиникалық практикаға белсенді түрде дамып, енгізілуде. Әдіс көптеген биологиялық объектілердің (ісік, микробтық жасушалар) химиялық заттарды – фотосенсибилизаторларды кумулизациялау қабілетіне негізделген, содан кейін олар күн сәулесіне, сондай-ақ толқынның белгілі бір ұзындығының лазерлік сәулеленуіне сезімтал болады. Фотосенсибилизатор сіңдірілген жасушаларда биологиялық жүйелерге деструктивті әсер ететін оттегінің синглетті формаларының генерациясымен бірге фотохимиялық процесс іске қосылады. Шолуда лазерлік медицинаның бір бағыты болып табылатын жарықты және химиялық қосылыстарды – фотосенсибилизаторларды кешенді қолдануға негізделген фотодинамикалық терапияны қолдану мәселелері бойынша мәліметтер берілген. ФДТ-ның қазіргі мүмкіндіктерін шолудың өзектілігі іріңді жараларды емдеуде осы әдісті қолдануға хирург мамандардың үлкен қызығушылығын тудырды. Мақалада емнің осы әдісін әзірлеу туралы қысқаша тарихи оң жағында келтірілген, оның әрекет ету принциптері мен механизмдері көрсетілген. Хирургиялық тәжірибеде фотодинамикалық терапияны қолдану мүмкіндіктері талданады. Іріңді-некрозды жараларды емдеу үшін әдісті одан әрі әзірлеудің перспективасы негізделеді.

Түйін сөздер: лазерлік медицина, фотодинамикалық терапия, фотосенсибилизатор, фотодинамикалық терапия, іріңді жара.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПРИ ЛЕЧЕНИИ ПАЦИЕНТОВ С ГНОЙНЫМИ РАНАМИ

Аннотация. В наши дни активно развивается и внедряется в клиническую практику относительно новая медицинская технология – фотодинамическая терапия. Метод основан на способности многих биологических объектов (опухолевые, микробные клетки) кумулировать химические вещества – фотосенсибилизаторы, после чего они становятся чувствительными к солнечному свету, а также лазерному излучению определённой длины волны. В клетках, которые абсорбировали фотосенсибилизатор запускается фотохимический процесс с генерацией синглетных форм кислорода, который обладает деструктивным влиянием на биологические системы. В обзоре представлены сведения по вопросам применения фотодинамической терапии, основанном на комплексном применении света и химических соединений – фотосенсибилизаторов, являющимся одним из направлений лазерной медицины. Актуальность обзора существующих возможностей ФДТ обусловлена большим интересом специалистов-хирургов к применению данного метода при лечении гнойных ран. В статье приведена краткая историческая справа о разработке данного способа лечения, освещены принципы и механизмы его действия. Анализируются возможности применения фотодинамической терапии в хирургической практике. Обосновывается перспективность дальнейшей разработки метода для лечения гнойно-некротических ран.

Ключевые слова: лазерная медицина, фотодинамическая терапия, фотосенсибилизатор, фотодинамическая терапия, гнойная рана.

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ISSN 2518-1629 (Online), ISSN 2224-5308 (Print)

http://biological-medical.kz/index.php/en/

Редактор *М. С. Ахметова, Т. М. Апендиев, Д. С. Аленов*
Верстка на компьютере *Д. Н. Калкабековой*

Подписано в печать 26.07.2019.
Формат 60х881/8. Бумага офсетная. Печать – ризограф.
4,2 п.л. Тираж 300. Заказ 4.

Национальная академия наук РК
050010, Алматы, ул. Шевченко, 28, т. 272-13-18, 272-13-19