

EFFECTIVENESS OF PHOTODYNAMIC THERAPY IN THE CORRECTION OF POSTACNE SCARS AND MORPHOFUNCTIONAL CHANGES IN THE SKIN

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Abstract

Acne is one of the most common dermatosis in young people. 85% of cases occur in patients between 12 and 24 years old. Duration of the disease, severe form, frequent recurrences of acne, autotraumatization lead to development of symptoms complex postural, manifested in the form of scarring changes, dyschromia, reduced elasticity, increased porosity and mildew. Acne complications occur in 95% of patients. Development of an effective method for the correction of acne complications is a topical problem of modern dermatology and cosmetology. The article describes the method of application of photodynamic therapy with an outer gel photosensitizer based on E6 chloride in patients with severe form of acne after prior treatment with systemic retinoids. The morphofunctional indicators of the skin and the composition of the microbiome in the dynamics were studied. As a result of the course of photodynamic therapy, resolution of scarring was observed in 97,2% of patients, disappearance of pigmentation on cheeks and skin on the forehead in 89,1% and 91,9% of patients respectively, restoration of elasticity in 100% of subjects, decrease in oiliness on the cheeks and skin in 91% and 94,5 % of patients respectively.

The exact exposure of the photosensitizing gel when applied externally to the scar tissue, the time range of its highest concentration and optimal duration of the procedure were determined. As a result of the application of photodynamic therapy, the skin relief was leveled, its oiliness decreased, the pigmentation disappeared and the elasticity was restored. In the microbiota of seborrheic sites, normal flora predominated over pathogenic. This method proved to be effective in the correction of the postural.

Keywords: photodynamic therapy, photosensitizer, chlorin e6, acne, retinoid, scar, microbium.

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ЭФФЕКТИВНОСТЬ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ В КОРРЕКЦИИ РУБЦОВ ПОСТАКНЕ И МОРФОФУНКЦИОНАЛЬНЫХ ИЗМЕНЕНИЙ КОЖИ

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Резюме

Акне является одним из самых распространённых дерматозов у лиц молодого возраста. В 85% случаев встречается у пациентов в возрасте от 12 до 24 лет. Длительность заболевания, тяжелая форма, частые рецидивы угревой болезни, ауотравматизация приводят к развитию симптомокомплекса постакне, проявляющегося в виде рубцовых изменений, дисхромии, сниженной эластичности, повышенного порообразования и милиумов. Осложнения акне встречаются у 95% больных. Разработка эффективного метода для коррекции осложнений акне является актуальной задачей современной дерматологии и косметологии. В статье описана методика применения фотодинамической терапии с наружным гелем фотосенсибилизатором на основе хлорина е6 у пациентов с тяжелой формой угревой болезни после предварительно проведенного лечения системными ретиноидами. Изучались морфофункциональные показатели кожи и состав микробиома в динамике. В результате проведенного курса фотодинамической терапии разрешение рубцов наблюдалось у 97,2% больных, исчезновение пигментации на щеках и на коже лба у 89,1% и 91,9% пациентов соответственно, восстановление эластичности у 100% исследуемых, уменьшение жирности на щеках и коже лба у 91% и 94,5% больных соответственно.

Была установлена точная экспозиция геля фотосенсибилизатора при наружном нанесении на рубцовую ткань, диапазон времени его наибольшей концентрации и оптимальной продолжительности процедуры. В результате применения фотодинамической терапии выровнялся рельеф кожи, уменьшилась ее жирность, исчезла пигментация, а эластичность восстановилась. В составе микробиома себорейных участков преобладала нормальная флора над патогенной. Данный метод оказался эффективным в коррекции постакне.

Ключевые слова: фотодинамическая терапия, фотосенсибилизатор, хлорин еб, акне, ретиноид, рубец постакне, микробиом.

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Introduction

Acne is a chronic, recurring disease of the sebaceous glands and hair follicles, characterized by comedones, pustules, and inflammatory infiltrates, most commonly occurring in young adults [1]. Antibacterial drugs (doxycycline), isotretinoin, and androgen receptor blockers (cyproterone acetate in combination with ethinyl estradiol as part of an oral contraceptive) are used to treat acne. For severe inflammatory acne in women, short courses of systemic glucocorticosteroids are used [1,2,3]. Topical retinoids (adapalene), benzoyl peroxide, antibacterial drugs (clindamycin phosphate), and combination medications are prescribed for topical therapy [1,4].

For severe acne and ineffective topical therapy, isotretinoin, a vitamin A derivative, is widely used. The drug suppresses sebaceous gland function, normalizes keratinization processes, has a pronounced anti-inflammatory effect, and reduces the appearance of post-acne scars. Isotretinoin is prescribed at an initial dose of 0.5 mg/kg of body weight per day, with a possible increase to 1.0 mg/kg. A cumulative dose of 120–150 mg/kg is required to achieve sustained remission. Dry skin and mucous membranes, reversible lipid metabolism disorders, and liver enzyme abnormalities often occur during treatment. Systemic retinoids, if necessary, are combined with antibiotics or hormonal drugs, which increases the overall effectiveness of treatment [1,3].

However, after a course of therapy, post-acne manifestations often remain in the form of post-inflammatory changes in the dermis, dyschromia, scars, enlarged pores, decreased skin elasticity, milia and atheromas, the severity of which depends on the severity and duration of acne [5].

Acne complications occur in 95% of patients, with 30% experiencing significant cosmetic defects, which can lead to psychological and social problems leading to social maladjustment [6]. Post-acne scars also often arise from auto-traumatization of the skin, untimely and/or inadequate treatment [7]. The main risk factors for the development of cicatricial changes include the

severity of the pathological process, the duration of the disease, and recurrence. Thus, patients with severe acne are 3.4–6.8 times more likely to develop scars than those with mild to moderate acne [8].

Atrophic scars arise from collagen breakdown in 80–90% of patients, while keloid and/or hypertrophic scars (due to decreased collagenase activity and excessive deposition of collagen types I and III) occur in 10–20% of patients [9]. Post-inflammatory hyperpigmentation is equally common in men and women at any age and results from melanin deposition in the epidermis or dermis following inflammation and skin trauma. It most often develops in individuals with Fitzpatrick phototypes IV–VI. Ultraviolet radiation increases the severity of hyperpigmentation [10].

The composition of the skin microbiome significantly influences the development of acne. High bacterial counts often cause acne recurrence [11].

Bacteria belonging to 4 types have been mainly identified on human skin: *Actinobacteria* (for example, *Corynebacterineae*, *Propionibacterineae*), *Firmicutes* (for example, *Staphylococcaceae*), *Proteobacteria* and *Bacteroidetes* [11]. The bacterial composition varies depending on age, body region, and microenvironment [12]. In seborrheic areas of the skin (face, scalp, chest, interscapular region), propionibacteria, which survive in anaerobic conditions, predominate [13]. Staphylococci and corynebacteria are more common on the moist skin of the armpits, groin, and popliteal fossa. Gram-negative bacteria predominantly colonize dry skin [14]. *Malassezia spp.* are distributed over the entire surface of the skin [15]. *Cutibacterium acnes* (*C. acnes*) accounts for approximately 85–90% of all identifiable microorganisms, dominates in the sebaceous hair follicle area, and is one of the factors in the pathogenesis of acne [16]. However, the number of *C. acnes* does not affect the development of severe acne [17].

Benzoyl peroxide and clindamycin (for topical therapy), isotretinoin and minocycline (for oral administration) reduce the bacterial load. For example, after 5 months of treatment, isotretinoin has been

shown to increase the number of *C. acnes* ribotypes with bactericidal activity [18,19].

Materials and Methods

A dermatological examination of 847 people aged 18-25 years revealed acne in 61.5%. Severe acne was diagnosed in 102 patients, most commonly in men. All patients with severe acne were treated with isotretinoin for an average of 8 to 10 months. Topical creams containing azelaic acid, adapalene, and benzoyl peroxide were applied. Additionally, skin morphofunctional parameters (moisture, oiliness, elasticity, pigmentation, pore formation) and bacterial count were measured.

The Multiskin Test Center MC 900 software and hardware system (Courage + Khazakaelectronic GmbH, Germany, registration no. 11629994, dated April 17, 2009) was used to evaluate the functional properties of the skin. Measurements were performed on pre-cleansed skin in a well-ventilated room at a temperature of 22°C and 40–60% humidity for 15–20 minutes. Sensors were placed on the medial forehead, the central area of the right cheek (under the zygomatic bone), and the medial chin [20,21].

Skin scrapings from the forehead were used for microbiological analysis. Samples were collected twice: before treatment and after a course of photodynamic therapy (PDT). The microbiome was studied using a classical bacteriological method. Cultivation was performed on enriched nutrient media, followed by colony counting (lg CFU/ml) under standard conditions [14].

To correct acne complications, PDT was used, a treatment method using an external photosensitizer gel (PS) and laser radiation, the wavelength of which corresponds to the peak absorption of PS [22]. The use of topical PS eliminated toxic and irritating effects. After activation of ultra-bright LEDs, cytotoxicity resulting from the photochemical reaction causes necrosis or apoptosis of the pathogenic cell. This results in the growth of young, healthy cellular structures, collagen and elastin synthesis, improved microcirculation, and restored skin pigmentation. The procedure is painless and non-invasive, with no downtime or side effects [23].

For PDT, an external photosensitizer gel was used, the active substance of which is the N-dimethylglucamine salt of chloride e6, obtained by extraction of chlorophyll A from the marine microalgae spirulina and its subsequent chemical transformation using the original technology [24]. Trade name of the drug: gel photoditazine (VETA-GRAND LLC, Russia, registration certificate no. FSR 2012/ 13043 dated June 08, 2017). The facial skin was pre-cleaned with an aqueous solution of chlorhexidine. The gel was applied to dry skin under occlusion and left for 10 minutes, then washed off with

water and a gel/foam cleanser, thoroughly cleansing the pores of the photodynamic reaction. To activate the photodynamic reaction, red laser radiation was used for 10 minutes in the range of 660 ± 2 nm. To irradiate the entire surface to be treated, a laser device (Latus-T, registration No. FSR 2010/09207, Russia) with a power of 1-1.5 mW/cm², cumulative energy of 100-180 J/cm² was used. The procedure was carried out once a week, with a total of 10 courses [22].

Results

Clinical cure of acne with the use of systemic retinoids was achieved in 97% of patients. However, when examining morphofunctional parameters of the skin, dehydration was detected in 92% of patients, increased oiliness of the cheeks and forehead in 83.7% and 78.3% of patients, respectively, low elasticity in 32.4% of patients, increased pore formation in the nose area in 27.2% of patients, cheeks in 36.3% of patients, forehead in 40.9% of patients, and hyperpigmentation on the cheeks and forehead in 64.8% and 45.9% of patients, respectively. Post-acne scarring was observed as complications in 37.3% of patients.

The following microorganisms were identified in the forehead skin microbiome before photodynamic therapy: *Staphylococcus spp.* (66.7% and 4.2 lg CFU/ml), *Staphylococcus aureus* (33.3% and 2.3 lg CFU/ml), *Micrococcus spp.* (58.3% and 3.3 lg CFU/ml), *Enterobacter spp.* (8.3% and 3.3 lg CFU/ml), *Klebsiella spp.* (8.3% and 2.2 lg CFU/ml), *Bacillus spp.* (8.3% and 1.6 lg CFU/ml), and *Candida spp.* (25% and 3 lg CFU/ml). Hemolytic *Staphylococcus spp.* (75% and 4.1 lg CFU/ml) and *Candida spp.* (25% and 2.6 lg CFU/ml) were also isolated.

After the course of PDT, scar resolution was observed in 97.2% of patients, disappearance of pigmentation on the cheeks and forehead skin in 89.1% and 91.9% of patients, respectively, restoration of elasticity in 100% of patients, and a decrease in oiliness on the cheeks and forehead skin in 91% and 94.5% of patients, respectively.

In the microbiological examination after PDT, the frequency of *Staphylococcus spp.* increased (up to 75% and 3.7 lg CFU/ml), while *Staphylococcus epidermidis* was found in 41.7% of cases in the amount of 4.3 lg CFU/ml, the prevalence of *Enterobacter spp.* increased (16.7% and 3.5 lg CFU/ml), *Candida spp.* (41.7% and 3.6 lg CFU/ml). Also, the frequency of hemolytic *Staphylococcus spp.* decreased (up to 33.3% and 2.8 lg CFU/ml) and *Candida spp.* (up to 8.3% and 2.7 lg CFU/ml), and *Staphylococcus aureus*, *Bacillus spp.*, and *Klebsiella spp.* completely disappeared. *Micrococcus spp.* remained constant (58.3% and 2.7 lg CFU/ml).

To more accurately determine the exposure of the PS gel to the skin and improve the effectiveness of PDT,

individual measurements of chlorin e6 fluorescence in the skin were performed in patients with cicatricial changes within 5-25 minutes, which can indirectly assess the accumulation of the photosensitizer gel (Table, Fig.).

According to the results of fluorimetry, the highest fluorescence intensity was determined in the range of 10-20 minutes, which determines the optimal exposure of the photosensitizer gel based on e6 chloride for 10 minutes, and the exposure time to laser radiation for 10 minutes.

Discussion

Long-term acne, severe acne, frequent acne recurrences, and autotraumatization lead to the development of post-acne symptoms, manifested as scarring, dyschromia, decreased elasticity, increased pore formation, and milia. The development of an effective method for correcting acne complications is an urgent task of modern dermatology and cosmetology. Many post-acne treatments are accompanied by soreness and require a period of rehabilitation. The article describes a technique for using PDT with an external photosensitizer gel based on e6 chloride in patients with severe acne after prior treatment with systemic retinoids. The positive dynamics of the morphofunctional parameters of the skin and the composition of the microbiome under the influence of PDT has been established. The exact exposure of the photosensitizer gel during external application to scar tissue, the time range of its highest concentration and the optimal duration of the procedure were determined. As a result of the application of PDT, the skin's relief was evened out, its oiliness decreased, pigmentation

Таблица

Динамика интенсивности флуоресценции после местного использования геля фотосенсибилизатора на основе хлорина е6

Table
Dynamics fluorescence intensity after topical application of chlorin e6 photosensitizer gel

Экспозиция геля (мин) Gel exposure (min)	Интенсивность флуоресценции (усл.ед.) Fluorescence intensity (units)
5	0,199
10	0,659
15	0,754
20	0,707
25	0,539

disappeared, and elasticity was restored. This method proved to be effective in correcting post-acne.

Conclusion

PDT resulted in the correction of scarring, pigmentation resolution, a decrease in oiliness, and restoration of elasticity. Using PDT with a topical gel based on chlorin e6 resulted in the restoration of the microbiome composition of seborrheic areas. The population of opportunistic microorganisms that produce pathogenic enzymes (hemolytic *Staphylococcus spp.* and *Candida spp.*, *Staphylococcus aureus*, and *Klebsiella spp.*) significantly decreased. However, an increase in *Staphylococcus epidermidis*, which adversely affects the development of acne, was observed.

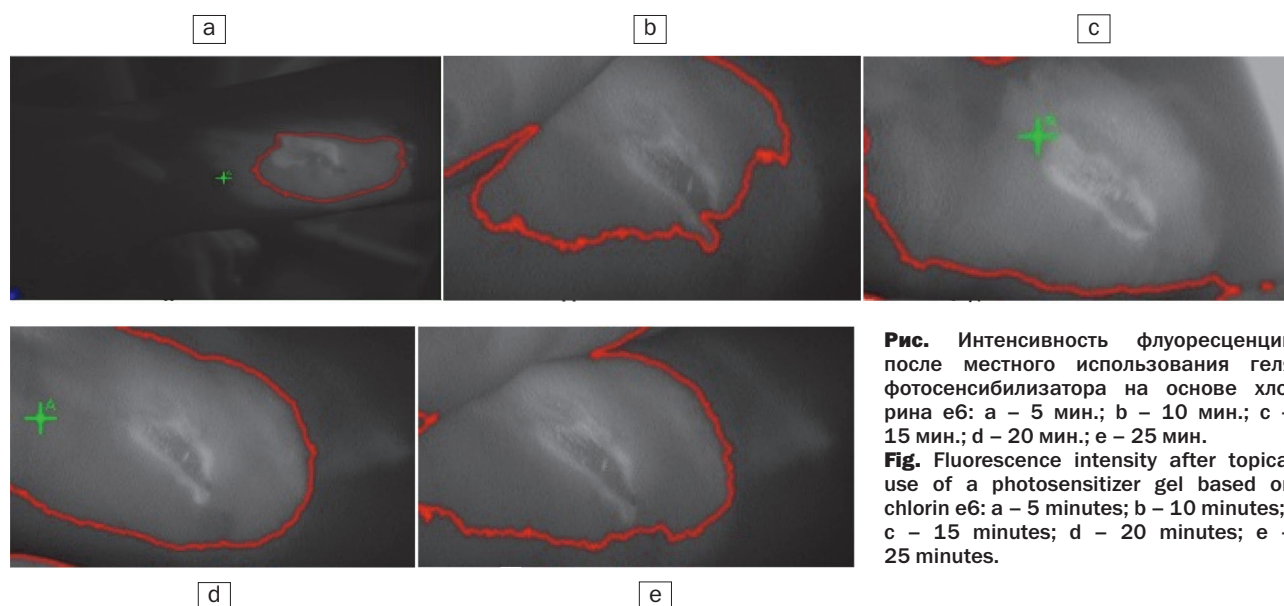


Рис. Интенсивность флуоресценции после местного использования геля фотосенсибилизатора на основе хлорина е6: а – 5 мин.; б – 10 мин.; с – 15 мин.; д – 20 мин.; е – 25 мин.

Fig. Fluorescence intensity after topical use of a photosensitizer gel based on chlorin e6: a – 5 minutes; b – 10 minutes; c – 15 minutes; d – 20 minutes; e – 25 minutes.

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