ORIGINAL ARTICLES

PHOTODYNAMIC REPARATIVE SKIN REGENERATION USING APPLICATION OF PHOTOSENSITIZER GEL BASED ON CHLORIN E6

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Abstract

The results of a study of the clinical effectiveness of the correction of involutional changes in the skin by the method of photodynamic therapy (PDT) with the use of a photosensitizer gel (PS), the active substance of which is the trismeglumine salt of chlorin e6, are presented. The data of fluorescence spectroscopy for monitoring the level of PS fluorescence in order to determine the optimal time of its exposure are demonstrated. The study of the optimal exposure time involved 80 patients with different skin phototypes. The study of the effectiveness of PDT involved 42 patients aged 44–68 years with signs of chrono- and photoaging. The PDT procedure was performed by irradiating the entire surface treated with the PS with a power density of 100 mW/cm^2, a light dose of 120–140 J/cm^2, a laser radiation wavelength of 660 nm, and a light beam area of 400–800 cm^2. It was found that exposure to PS for 10–20 min gives the highest fluorescence and does not depend on the skin phototype. The clinical effect of PDT was achieved in 85.7% of patients; there were no negative subjective sensations. Moisture metrics increased on the skin of the face by 53%, reaching the control values in young healthy volunteers, on the skin of the hands - by 64%. Elastometry indicators on the skin of the face and hands increased by 19% and 16%, respectively. Thus, the PDT procedure with PS based on chlorin e6 is an effective method for correcting involutional changes in the skin, leads to a pronounced clinical effect, improves the parameters of skin moisture measurement and elastometry, and passes without undesirable local reactions. Optical coherence tomography showed an increase in collagen ordering.

Keywords: optical coherence tomography, moisture measurement, elastometry, photodynamic therapy, photosensitizer, involutional changes in the skin, aging, trismeglumine salt of chlorin e6.

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ФОТОДИНАМИЧЕСКАЯ РЕПАРАТИВНАЯ РЕГЕНЕРАЦИЯ КОЖИ С ПРИМЕНЕНИЕМ НАРУЖНОГО ГЕЛЯ–ФОТОСЕНСИБИЛИЗАТОРА НА ОСНОВЕ ХЛОРИНА Е6

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Резюме

Представлены результаты изучения клинической эффективности коррекции инволюционных изменений кожи методом фотодинамической терапии (ФДТ) с применением геля–фотосенсибилизатора (ФС), активным веществом которого является трисмеглюминовая соль хлорина е6. Продемонстрированы данные флуоресцентной спектроскопии для контроля уровня флуоресценции ФС с целью определения оптимального времени его экспозиции. В исследовании оптимального времени экспозиции участвовали 80 пациентов с различным фототипом кожи. В исследовании эффективности ФДТ участвовали 42 пациента в возрасте 44–68 лет с признаками хроно– и фотостарения. Процедуру ФДТ выполняли путем облучения всей обрабатываемой ФС поверхности с плотностью мощности 100 мВт/см^2, световой дозой 120–140 Дж/см^2, длина волны лазерного излучения 660 нм, площадь светового пучка 400–800 см^2. Установлено, что экспозиция ФС в течение 10–20 мин дает наибольшую флуоресценцию и не зависит от фототипа кожи. Клинический эффект ФДТ достигнут у 85,7% пациентов, субъективных ощущений негативного характера не отмечалось. Показатели влагометрии увеличились на коже лица на 53%, достигнув контрольных значений у молодых здоровых добровольцев, на коже кистей рук – на 64%. Показатели эластометрии на коже лица и рук увеличились на 19% и 16%, соответственно. Таким образом, процедура ФДТ с ФС на основе хлорина е6 является эффективным методом коррекции инволюционных изменений кожи, приводит к выраженному клиническому эффекту, улучшает показатели влагометрии и эластометрии кожи и проходит без нежелательных местных реакций. При оптической когерентной томографии установлено увеличение упорядоченности коллагена.

Ключевые слова: фотодинамическая терапия, фотосенсибилизатор, трисмеглюминовая соль хлорина е6, инволюционные изменения кожи, старение, оптическая когерентная томография, влагометрия, эластометрия.

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Introduction

Photodynamic therapy (PDT) is a treatment method based on the use of photosensitisers (PS) and laser radiation with a wavelength corresponding to the PS absorption peak. Despite the fact that research into the application of PDT has been going on for many years, the use of this method in aesthetic medicine and dermatovenerology was restrained by the lack of sufficiently effective topical non-toxic drugs that do not have a strong local irritating effect. The emergence of PS for topical use and radiation sources for activating PS based on superbright LEDs have opened up new ways to solve urgent problems of dermatovenerology and cosmetology [1–3].

Cytotoxicity resulting from a photochemical reaction leads to cell necrosis or apoptosis. As a rule, in situations where oxidative destruction of mitochondria occurs, apoptosis is observed, with destruction of the cell wall, necrosis predominates. After damage, the body's response is aimed at removing either the remnants of the cell after apoptosis, or damaged tissue and the restoration of the surrounding structures after necrosis. The cascade of cytotoxic and inflammatory reactions, as well as the mechanisms of damage restoration, have now been studied in sufficient detail [1, 4, 5].

PDT was most often used in oncology, and therefore the mechanism of its action is best studied in the treatment of patients with oncological diseases. Gradually, the literature accumulated data on a kind of "side" effect of PDT in cancer patients in the form of skin lightening, increased skin elasticity, disappearance of fine wrinkles, which prompted the use of the method to correct involutional skin changes [1, 4–6].

Purpose of the study: to study the clinical efficacy of PDT with the use of PS, the active substance of which is the trismeglumine salt of chlorin e6, as a method of correction involutional skin changes. Evaluation of the effectiveness of PDT was carried out according to changes in the physiological parameters of the skin using elastometry, moisture measurement..

Materials and methods

Study organisation. The study was carried out on the basis of the Department of Dermatological Oncology and Laser Surgery of the Central Clinic of the Russian Academy of Sciences, the Medical Center for Cosmetic Correction "ECLAN", Russian National Research Medical University named after N.I. Pirogov, State Budgetary Healthcare Institution "Moscow Research and Practical Center for Dermatovenereology and Cosmetology of the Moscow Department of Health" (Moscow), the clinical base of the Department of Dermatology and Venere-

ology with the course of cosmetology of the Tver State Medical University of the Russian Ministry of Health (Tver) "Professorial Clinic".

Patients and volunteers participating in the study. The research design included two independent directions. The first is aimed at establishing the optimal exposure time of a gel containing chlorin e6 by fluorescence spectroscopy in healthy volunteers (80 people). They also had their indicators of elastometry and moisture measurement measured, which served as reference values in the second direction of the study.

The second direction consisted in the correction of involutional skin changes by PDT with PS based on chlorin e6. The study involved 42 patients, including

Таблица 1
Общая медико-социальная характеристика обследованных лиц
Table 1
Combined medical and social assessment of the patients

Показатели Results	Группа I, n=42 Group I, n=42	Группа II, n=80 Group II (n=80)	Уровень значимости различий Differences significance value
Возраст, лет Age, years	54 (48–62)	32 (25–38)	<0,001
Пол (мужчины/женщины) Sex (male/female)	10/32	18/62	0,87
Вредные привычки Cacoethes			
Курение Smoking	28 (67)	33 (41)	0,008
Употребление алкоголя Alcohol ingestion	31 (738)	55 (69)	0,56
Употребление сладкого/мучного Sweet/farinaceous food ingestion	40 (95)	47 (59)	<0,001
Гиподинамия Sedentary lifestyle	13 (31)	20 (25)	0,044
Сопутствующая патология Comorbidity			
Сердечно–сосудистые заболевания Cardiovascular disease	40 (95)	22 (28)	<0,001
Заболевания мочеполовой системы Diseases of genitourinary system	3 (7)	17 (21)	0,046
Заболевания эндокринной системы Diseases of endocrine system	16 (38)	6 (8)	<0,001
Заболевания опорно–двигательной системы Diseases of musculoskeletal system	25 (60)	5 (6)	<0,001
Заболевания пищеварительной системы и печени Gastrointestinal and hepatic diseases	26 (62)	34 (43)	0,042
Глазные болезни Eye diseases	14 (33)	29 (36)	0,75
Отягощенный аллергоанамнез Positive allergic anamnesis	19 (45)	24 (30)	0,09
Дерматологические характеристики Dermatologic characteristics			
Фототип кожи Skin phototype			
2–й 2nd	32 (76)	58 (73)	0,09
3–й 3rd	7 (17)	14 (18)	0,91
4–й 4th	3 (7)	8 (10)	0,60

32 women and 10 men aged 44–68 years, average age 54±5 years, with signs of chrono- and photoaging.

The medical and social characteristics of the study participants are presented in Table 1. There was a difference in the rates and frequency of conditions indirectly associated with age, a decrease in lifestyle activity, a higher incidence of concomitant diseases distinguished patients from volunteers. Frequency weights of skin types did not differ significantly.

Photosensitizer. For PDT, a photosensitizer gel was used, the active substance of which is the trismeglumine salt of chlorin e6, obtained by the extraction of chlorophyll A from the marine microalga spirulina and its subsequent chemical transformation using an original technology. Trade name of the drug: gel "Chloderm", containing 0.2% Chlorophylin - CI 75810 as an active substance. Manufacturer: Areal OOO, Russia (EAEU Declaration of Conformity No. RU D-RU. AYU18.B.08190).

Study design. Simultaneous transverse in the case of studying the optimal exposure time of the gel with PS in healthy volunteers. An open prospective study of the effectiveness of PDT for the correction of involutional skin changes.

Criteria for inclusion in the study of the effectiveness of PDT:

- the age of the examined is 40 and older;
- the presence of skin photoaging symptoms;
- desire to participate in the study, confirmed by the informed consent of the subject.

Exclusion criteria:

- the presence of concomitant pathology in patients at the stage of decompensation;
- pregnancy and lactation period;
- severe infectious processes (HIV infection, tuberculosis, syphilis, progressive course of viral hepatitis B and C);
- other local treatment, parallel undergoing of other anti-aging procedures;
- history of epilepsy;
- diseases accompanied by increased skin photosensitivity, porphyria or previously identified sensitivity to porphyrins; taking photosensitizing medication;
- voluntary refusal of subjects to participate in the study.

Ethical aspects of the study. The clinical study was conducted in accordance with the legal and regulatory requirements and with the general principles set out in the International Ethical Rules for Biological and Medical Investigations with Human Participation (Council of International Medical Scientific Organizations, 2002); in accordance with the rules of Good Clinical Practice (International Conference on Harmonization, 1996) and with the World Medical Association's Declaration of Helsinki (as amended by the 64th General Assembly of the WMA, Fortaleza, Brazil, October 2013). Each of the participants signed a voluntary informed consent.

Spectroscopic research technique. A gel with PS was applied to the cleansed skin. In the interval of drug exposure from 5 to 30 min, a part of the gel was removed from the edge of the skin every 5 min, and fluorescence spectroscopy was performed to assess the intensity of PS fluorescence. The "Spectrum-Cluster" installation was used (registration certificate No. ФС P2011/10331 dated March 31, 2011).

PDT technique. The PS was applied to previously cleansed and dried skin of the face entirely, and to hard-to-reach areas - with a cotton swab. The PS was kept under the film for 15 min, then washed off with water with a cleansing gel/foam, thoroughly cleaning pores from PS. Then, at the same time, frontally at a distance of 5–10 cm from the lamps, the entire treated surface was irradiated with a "Maska" laser device (LATUS-T series, Atkus OOO, Russia) with a power density of 100 mW/cm^2, a light dose of 120–140 J/cm^2. The wavelength of the laser radiation corresponded to 660 nm, the area of the light beam was 400–800 cm^2.

To assess the clinical effectiveness of the method, objective parameters were assessed by measuring skin moisture and elastometry. Multi Skin Test 900 apparatus, which has sensors for monitoring the following functional parameters of the skin, was used: moisture (hydrometry) - moisture sensor (corneometry method), which allows to assess the water content in the stratum corneum; elasticity - the elasticity sensor (kutometry method) allows to objectively measure the elasticity of the skin. The reference values were the indicators of the skin condition of healthy volunteers.

Optical coherence tomography (OCT) technique. Cross-polarization modification of OCT (CP-OCT) made it possible, in addition to standard information on the structure of the skin, to obtain information on the properties of tissue in relation to light depolarization. For a quantitative assessment of diagnostic CP–OCT images in order to characterize the state of collagen, the integral depolarization factor (IDF) was used [9–11]. The less frequent and more fragmented collagen bundles in the skin, the lower the IDF value.

Statistical processing of results. Statistical processing of results was carried out using the Statistica for Windows 6.0 software package. Data were presented as median and interquartile range for quantitative measures and calculated frequency for qualitative measures. To assess the difference in means in pairwise unrelated samples, the Mann – Whitney U test was used, multiple comparisons were performed using the Kruskal–Wallis H test (comparison of data from three samples). The chi-square test was used to test the significance of differences in qualitative variables. If the achieved level of differences significance did not exceed 0.05, they were considered accurate [12].

Results

Spectroscopic study of the exposure time to PS in healthy volunteers. Comparative analysis using the Kruskull – Wallis test made it possible to conclude that the fluorescence intensity of the gel varies depending on the skin type (Table 2). However, for each skin type, the maximum fluorescence indicators were recorded at exposure to PS for 15 min. After 20 min, fluorescence indices decreased ($p < 0.05$) in all three observation groups, differing in skin phototype. With a further increase in the exposure time, the fluorescence indices in the groups did not differ significantly ($p > 0.05$). Thus, exceeding the exposure for more than 15 minutes was considered inappropriate.

Study of the response to PDT. The clinical effect of PDT was achieved in 85.7% of patients (36 people), no visible changes were observed in 14.3% of cases (6 people). No adverse skin reactions or worsening of the skin condition have been reported. The PDT procedure was not accompanied by negative subjective feelings. The resulting aesthetic effect after the procedures was confirmed by objective research methods, such as moisture measurement, elastometry, and was expressed in smoothing of fine wrinkles, increasing of the elasticity and skin hydration. Taking into account the difference in median values, moisture measurements increased in the face skin by 53%, in the hands skin - by 64%. At the same time, according to the moisture measurement on the face skin after PDT, no differences were revealed when compared with the control group (healthy volunteers), and in the hands skin the differences after therapy were statistically significant. Elastometry indicators in the face and hands skin increased by 19% and 16%, respectively, which was comparable with the elastometry indicators in healthy volunteers (Table 3).

Quantitative processing of CP – OCT images obtained during PDT monitoring showed the ordering of collagen fibers after therapy (Table 4).

The changes dynamics in the value of IDF during CP-OCT after a PDT course carried out in a 55-year-old patient is shown in Fig. 1. It can be seen that after the course of PDT, the OCT signal in orthogonal polarization increases, which indicates an increase in the amount of ordered collagen in the studied skin, and, therefore, indicates the success of the treatment course.

Visual changes in the skin condition in two patients after the PDT course are shown in Fig. 2-3..

Таблица 2
Показатели флуоресценции геля–фотосенсибилизатора в зависимости от времени экспозиции при разных фототипах кожи, Me (Q25% – Q75%), усл. ед.
Table 2
Fluorescence of the photosensitizer gel depending on exposure time on different skin phototypes, Me (Q25% – Q75%), arbitrary units

Время экспозиции геля–фотосенсибилизатора (мин) Time of exposition of photosensitizer gel (minutes)	Флуоресценция фотосенсибилизатора Fluorescence of photosensitizer			Уровень значимости различий показателя флуоресценции Differences of fluorescence significance value
	II фототип кожи (n=58) Skin phototype II (n=58)	III фототип кожи (n=14) Skin phototype III (n=14)	IV–V фототипы кожи (n= 8) Skin phototypes IV–V (n=8)	
5	1,35 (1,29–1,38)	2,0 (1,66–2,09)	1,48 (1,17–1,69)	H=7,3 (p=0,026)
10	1,67 (1,55–1,72)	2,29 (1,95–2,31)	2,10 (2,04–2,19)	H=7,2 (p=0,027)
15	1,95 (1,88–1,99)	2,50 (1,92–2,61)	2,60 (2,06–2,72)	H=6,8 (p=0,032)
20	1,67 (1,55–1,69)	2,29 (1,98–2,34)	2,04 (1,78–2,18)	H=9,3 (p=0,009)
25	1,47 (1,39–1,52)	1,88 (1,76–1,98)	1,69 (1,55–1,74)	H=7,2 (p=0,027)
30	1,32 (1,27–1,48)	1,65 (1,55–1,69)	1,63 (1,58–1,70)	H=6,9 (p=0,032)

Таблица 3
Сравнительная оценка влагометрии и эластометрии в виде Me (Q25% – Q75%), усл. ед.
Table 3
Comparative assessment of moisture measurements and elastometry presented as Me (Q25% – Q75%), arbitrary units

Показатели, единицы измерения Results, units of measurement	Группа I Group I		p_1	Группа II (здоровые лица) Group II (healthy)	p_2	p_3
	До лечения Before therapy	После лечения After therapy				
Кожа лица Facial skin						
Влагометрия (корнеометрия) Moisture measurement (corneometry)	32 (29–34)	49 (44–53)	**0,017**	52 (46–58)	**0,011**	0,22
Эластометрия Elastometry	0,52 (0,48–0,56)	0,62 (0,48–0,65)	**0,034**	0,65 (0,59–0,70)	**0,032**	0,54
Кожа кистей рук Hands skin						
Влагометрия (корнеометрия) Moisture measurement (corneometry)	28 (25–31)	46 (40–51)	**0,009**	53 (48–55)	**0,012**	**0,047**
Эластометрия Elastometry	0,38 (0,32–0,41)	0,44 (0,40–0,49)	**0,029**	0,49 (0,47–0,53)	**0,027**	0,09

Таблица 4
Сравнительная оценка показателей интегрального фактора деполяризации в виде Me (Q25% – Q75%), ед.
Table 4
Comparative assessment of integral depolarization factor results presented as Me (Q25% – Q75%), units

Показатели, единицы измерения Results, units of measurement	Группа I Group I		p_1	Группа II (здоровые) Group II (healthy)	p_2	p_3
	До лечения Before therapy	После лечения After therapy				
ИФД кожи лица Integral depolarization factor of facial skin	0,02 (0,01–0,02)	0,05 (0,02–0,06)	**0,016**	0,09 (0,07–1,00)	**0,001**	**0,008**
ИФД кожи кистей рук Integral depolarization factor of hands skin	0,03 (0,01–0,03)	0,05 (0,02–0,06)	**0,044**	0,08 (0,08–0,09)	**0,007**	0,15

Примечание: p_1 – разница между показателями до и после лечения; p_2 – между показателями до лечения и здоровыми лицами; p_3 – между показателями после лечения и здоровыми лицами.
Note: p_1 – the difference between results before and after treatment; p_2 – the difference between results before treatment and healthy respondents; p_3 – the difference between results after treatment and healthy respondents.

Conclusion

It was found that the highest fluorescence is obtained by exposure of the gel-photosensitizer based on chlorin e6 for all skin phototypes for 10–20 min, the peak value of fluorescence was noted at the 15th minute of exposure.

PDT with an external gel-photosensitizer based on chlorin e6 in order to correct age-related changes in the skin of the face and hands leads to a pronounced clinical effect in 85.7% of patients. Concurrently, the indicators of moisture measurement and elastometry are objectively changed. Coherent tomography showed an increase in the amount of ordered collagen. The deterioration of the condition and adverse reactions on the skin were not registered. The data obtained from a clinical study in 42 patients indicate the efficacy of PDT with an external photosensitizer gel in chronoaging of the skin.

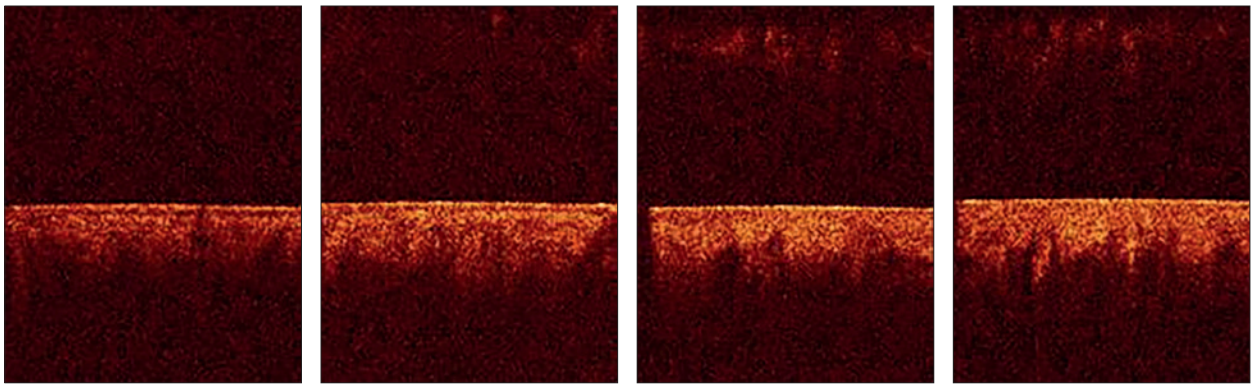

Рис. 1. Клинический пример эффекта ФДТ, проиллюстрированный визуализацией сигнала КП–ОКТ:
a – до курса ФДТ;
b – через 2 нед после курса ФДТ;
c – через 4 нед после курса ФДТ;
d – через 8 нед после курса ФДТ.
Fig. 1. Clinical example of the PDT effect illustrated by visualization of the cross-polarized-OCT signal:
a – before the PDT course;
b – 2 weeks after the PDT course;
c – 4 weeks after PDT course;
d – 8 weeks after the PDT course.

Рис. 2. Состояние кожи лица пациентки 49 лет:
a – до курса ФДТ;
b – через 8 нед после курса ФДТ.
Fig. 2. The condition of the facial skin of the patient, 49 years old:
a – before the PDT course;
b – 8 weeks after the PDT course.

Рис. 3. Состояние кожи лица пациентки 66 лет:
a – до курса ФДТ;
b – через 8 нед после курса ФДТ.
Fig. 3. The condition of the facial skin of the patient, 66 years old:
a – before the PDT course;
b – 8 weeks after the PDT course.

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