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Application of Cryogenic Methods in Skin Diseases of Different Etiology

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Additional information is available at the end of the chapter

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Abstract

The modern demand for effective treatment options in dermatology was successfully addressed by the invention of cryogenic method. By 2009, Dr. V.I. Kochenov had developed and patented cryogenic set of instruments based on 30 years of his personal clinical experience. The set includes a number of instruments, which could be used independently. It allows implementing a wide range of therapeutic and surgical procedures and has no commercially available alternatives. The main applications of the set include cryogenic revitalization, and treatment for such common dermatological ailments as psoriasis, warts, acne, hypertrophic scars, purulent diseases of the skin and subcutaneous fat, epithelial cysts, skin hemangiomas, precancerous skin lesions, and even malignant melanoma of the skin. A brief overview of etiology, classification and pathogenesis of these maladies is presented alongside with the step-by-step guidelines to cryo-exposure procedures. Not only guidelines but also comprehensive theoretical and practical training is provided to physicians at the center which was established at Nizhny Novgorod State Medical Academy. Physicians at Scientific Clinical Center of Medical Cryology "OnKolor" have been using the set, which proved to be effective even in the most difficult and otherwise costly cases. The procedures that have pronounced cosmetic effect, leaves no scars and dark spots.

Keywords: cryosurgery, cryotherapy, premalignancy, melanoma, acne, hemangioma, treatment dermatologic diseases

1. Introduction

Today, cryogenic treatment method is worth being applied much more widely than it occurs in reality. Paradoxically, cryosurgery has its opponents, despite the fact that this method has almost no complications, and its high efficiency in many situations based deeply in physiology and immunology puts it above traditional treatment methods. Cryodestruction differs favorably from all known methods of active treatment by properties such as, for example, complete ablasticity in the treatment of malignant tumors, natural immunostimulating effects, and organotypic regeneration.

The main objective of the cryosurgical method can be defined as the absolute destruction of pathological cells in a given volume of living tissue without damaging the normal, healthy cells around this tissue.

The effectiveness of cryosurgery has been demonstrated primarily in such areas of medicine as dermatology. In 1938, the first in-depth clinical study was published—a book by M.A. Beridze “About the use of cryotherapy in dermatology,” where the method was described imaginatively and in detail and the long-term treatment outcomes were presented. The author noticed that the removal of skin neoplasms with dry ice does not leave scars, and made recommendations on the proper use of cryotherapy.

Cryosurgery studies were carried out in almost all areas of medicine. Among these new technological developments in medical cryology, the most notable are cryogenic treatment methods patented by Scientific Clinical Center of Medical Cryology “OnKolor,” which have a very diverse range of medical applications. In Nizhny Novgorod State Medical Academy (Rector—Prof. B.E. Shakhov) and Scientific Research Institute of Applied and Fundamental Medicine (Director—Prof. S.N. Tsybusov), cryogenic methods of treatment are applied in otorhinolaryngology, gynecology, dermatology, oncology, and proctology (implemented by the medical team under the leadership of Prof. S.N. Tsybusov and Dr. V.I. Kochenov).

A “Set of instruments for medical cryology by Dr. V.I. Kochenov” was developed and approved by the Ministry of Health of the Russian Federation in 2009. This invention allows implementing all the available and a number of new treatment technologies in medical cryology in any area of clinical medicine. A center for theoretical and practical training was established at Federal State Budgetary Educational Institution of Higher Education “Nizhny Novgorod State Medical Academy,” Ministry of Health of the Russian Federation, where physicians of any clinical specialty relevant to medical cryology can take comprehensive training including new patented technologies using this set of instruments.

The set of instruments for medical cryology was developed upon 30 years personal experience of Dr. V.I. Kochenov, holder of second-level doctorate degree in Medical Sciences, certified physician of highest category, Co-chairman of All-Russian cryosurgical society, ISC member, inventor, and Director of Scientific Center of Medical Cryology “OnKolor.” All components of the set passed long-term clinical testing. This set of instruments for medical cryology is unique (never manufactured previously), all cryo-instruments have the original design and each is protected by the RF patent. Its composition is ample for diverse applications in medical cryology: cosmetology, dermatology, otolaryngology, stomatology, surgery, proctology, gynecology, oncology and other areas of clinical medicine.

Patented cryo-exposure techniques are based on the phenomenon of liquefaction of the ambient oxygen fraction, which creates the effects of cryo-oxygen saturation, cryo-oxygenation in pathologically altered tissues, as well as cryo-oxy-cavitation and cryo-ozone destruction of neoplasms, and have contributed significantly to the treatment of visually localized tumors.

The set includes: cryoclamps of various modifications—their design allows for the radical elimination of pathologically altered tissues; a cryospray unit with various nozzles; ring-shaped cryoapplicators with different ring opening and a tube; ring-shaped magnets with an opening; cryotrocar; Dr. V.I. Kochenov's cryogenic device "Ledok" (Icelet) with cannulas of different diameters; tampons for deep cryogenic massage with a meshed-cellular elastic surface and inserted thermal accumulators; a roller placed on the handle for cryosurgical massage; cryosticks with different configurations of the working surface; and a device for columnar cryobiopsy of the frozen tissue.

These instruments were developed for the purposes of medical cryology and have no commercially available alternatives. The set allows for implementing multiple new techniques of cryotherapy and cryosurgery, which expands the horizon of possibilities of medical cryology. An essential advantage of the set is that all instruments can operate independent of the power supply, that is, in a standalone mode.

2. Cryogenic revitalization in cosmetology

It is indisputable that treating any pathological process on the skin and especially the facial skin should be performed with cosmetic method. First and foremost, these requirements are adequately met by cryogenic therapy methods. However, cosmetologists should not take them simplified and consider cryogenic exposures as the basic techniques having only functional mechanisms of medical effect.

A great mistake in the activity management of beauty salons is to give charge over implementation of cryogenic procedures to the hands of nursing staff and such approach should be absolutely avoided. Cryogenic techniques intended for skin exposure are exclusively medical procedures.

When working with cryo-exposure techniques, we need to remember that liquid nitrogen is not the same piece of ice like a chamomile infusion frozen in a domestic refrigerator, which can hardly injure the facial skin look. Only the non-contact volatile exposure to liquid nitrogen vapors can be absolutely safe. Any skin application, even very brief (especially if done with cotton wool soaked in liquid nitrogen), if applied in the presence of skin moisture or sebaceous secretions, in case of sensitive or aging skin, will lead to adhesion, uncontrolled heat transfer, glaciation in the form of a solid spot and can end eventually with the formation of bubbles, necrosis, hyper- and hypopigmentation, and subsequently to hyperplastic scars.

To avoid such implications and create deep regenerative pulses in the skin through the actual formation of interstitial ice, the best proven technique is used and tested in clinical practice for many years—a technique of deep rejuvenation by cryo-kneading with special tampons with mesh embossed surface ("Method of cryogenic treatment of skin," a technique developed by Dr. V.I. Kochenov). It prevents the accidental creation of a drain freezing zone on the skin, which would have ended in the development of cryonecrosis and complications are

almost excluded. The objectives can vary very widely, from mild stimulation of blood supply and reviving complexion during the day or before going to the theater, to the elimination of hyperpigmentation and superficial keratoses, elimination of fine mesh of wrinkles, and skin smoothing in 3–4 weeks after the procedure. It depends on the degree of exposure, velocity of skin kneading performed with the tampon chilled in liquid nitrogen, and the number of cryo-exposure repetitions at a particular site.

Therapeutic effects come even from a very short-term skin freezing: exfoliation of the upper skin layer is facilitated; skin pores are reduced; blood vessels' tone is increased, and production of the innate skin collagen is stimulated. Longer freezing destroys viral manifestations and pathogenic microbial associations.

To provide a focused local effect, any cryo-spray device is suitable, if the distance to the tissue surface is increased and manipulation is performed in a pulse mode with close visual inspection of the treated surface.

The workplace of cryo-cosmetologist should be equipped not only with cotton sticks and a vacuum flask. To perform any cryological therapeutic intervention, destroying pathological tissue with a wadding stick is simply careless in our days.

The objective of the suggested method of cryogenic skin exposure described in this book is to provide a pronounced and persistent medical cosmetic effect without the risk of complications. The proposed method ensures:

- marked and long-lasting therapeutic cosmetic effect;
- possibility to control the treatment quality and effectiveness, due to the available clear criteria for assessing the zone and timing of cryo-exposure;
- excluded formation of skin vesicles and bullae;
- individual and differentiated approaches to treatment;
- rapid and non-traumatic freezing of the upper skin layers;
- dosed, with the possibility of precise localization and, ultimately, uniform and deep skin freezing;
- creation of discrete linear, non-merging freezing zones, with the direct formation of interstitial ice;
- complete cryosurgical destruction (cryodestruction) of individual minor pathological, exophytic and diffuse formations, and pigmentary changes; and
- possibility of multiple actual skin freezing without the risk of complications and cosmetic defects after the procedure.

A beauty salon that offers cryological procedures in its list of services needs an accessible set of devices to implement medical cryology techniques for facial skin rejuvenation. To perform cryoablation of pathological formations, cryo-cosmetologists are recommended to use "Ledok" (Icelet) unit with cannulae of different diameter.

The proposed set of spherical cotton tampons retain their elasticity at liquid nitrogen temperature and are encapsulated in natural fabric (textile—cotton, wool—with a checkered relief (waffle) structure, or braided, netlike, perforated leather). Capsules should have cells of different size, for example, a structure where the wall thickness between the cells does not exceed $\frac{1}{10}$ and the cell depth— $\frac{1}{5}$ of the cell side, respectively. Diameter of applicators can be correlated conveniently with the known morphological features of the human face, for example, the size of the optic fissure. The set should include tampons of at least three sizes, with diameters corresponding to the entire length, $\frac{1}{3}$ and $\frac{1}{5}$ of the patient's optic fissure. Capsules for three tampons of the same diameter are selected in such a way that the cell size for each tampon makes $\frac{1}{10}$, $\frac{1}{20}$, and $\frac{1}{30}$ of its circumference, and this pattern is kept for tampons of all three diameters, as follows from their practical use. A cotton wad is tightly crumpled, covered with a piece of textile under tension to form a ball-shaped tampon. The tampon is fixed, for example, by capturing the gathered textile elements in the proximal part of the tampon with a surgical clip on a thermally nonconductive handle.

2.1. Cryo-exposure procedure

Before starting treatment, the patient's skin is treated with an alcohol-free facial cleanser. Then a moisturizer is applied to the skin and gently rubbed in a circular motion. Wait for 10–15 minutes.

The first step is the pointwise cryodestruction of pigmented spots and minor benign skin tumors (papillomas and hemangiomas) by special applicators.

Then all tampons are immersed in the working container with liquid nitrogen. When rapid boiling of liquid nitrogen is stopped, tampons are ready for use.

Next, the tampon of the largest diameter and the largest cell size is taken from the liquid nitrogen and its excess is removed from the tampon. This tampon is used for test applications on the places, where the skin surface is the smoothest: the forehead or the chin. The tampon is rolled with its lateral surface, applying a gentle pressure on it and stretching the skin. The handle should be oriented at a very acute angle to the skin surface, thus making the rotation of the tampon archwise, almost by 180° . Thus, the tampon is rolled by a distance approximately equal to the half of its circumference. The average time of the tampon move is selected from 2–3 to 3–5 seconds depending on the skin type (sensitive or oily skin). After completing rotational rolling, the tampon leaves behind it an ellipsoidal relief imprint—the freezing zone. The surface of this zone is examined using a binocular magnifier and fiber optic lighting, and its characteristics are evaluated.

Next, two to three test applications are performed in the same way, rolling the tampon at different velocity, changing the angle of the handle and under control of thawing time, which should not exceed 1–3 seconds. Then the visual characteristics of the resulting zones are compared and the optimal rolling speed is selected, for which the freezing zone structure fully corresponds to the characteristic pattern of the tampon capsule. Upon completed cryomassage, the imprint fully disappears from the skin surface, due to the natural heat uptake.

Cryomassage of the face, neck, and décolleté is performed with the optimal selected velocity, following the basic rules:

- a single, one-time selected tampon is used for three to five applications; then it must be cooled by immersing in liquid nitrogen for 5–10 seconds, squeezed out and used further;
- the rolling direction during the cryo-exposure on the same section of the skin surface is changed along the line of visible skin folds and in short movements perpendicular to them.

When all the desired skin areas are subjected to cryo-exposure with a tampon of $\frac{1}{10}$ circumference cell size, the same areas are treated with tampons of $\frac{1}{20}$ and then $\frac{1}{30}$ circumference in the same way. As a result, a marked skin hyperemia appears 5–10 minutes after exposure, which is manifested in elongated spots on the places that were first subjected to cryo-exposure. During repeated massage of cryoapplications on hyperemic skin areas, the rolling velocity should be slightly reduced, and the freezing time in each point of the skin surface should be increased, respectively. Subsequent cryo-massage applications are oriented to those areas, where the hyperemia is less pronounced or has not yet developed.

Cryomassage for the less accessible facial skin areas (parotid region, nose bridge and wings, around the nostrils, around the lips, upper and lower eyelid, and eye corners) should use applicators as follows.

First, cryo-manipulations are performed with tampons of the large cell size: a tampon with a diameter of $\frac{1}{3}$ of the optic fissure is applied to the skin in the superciliary region, the nose bridge, the parotid region, and around the lips; a tampon with a diameter of $\frac{1}{5}$ of the optic fissure is applied to the skin around the nose wings, the nostrils, eyelids, and the internal and lateral angle of the eye; cryo-manipulations along the line of the most pronounced skin folds are performed with the same tampon. In doing so, the skin is stretched preliminarily with the other free hands in the direction perpendicular to the tampon rolling line, smoothing the wrinkled tissues and opening the skin folds for cryo-exposure. Ensure that the checkered relief freezing zone is formed on the stretched skin areas. Then cryomassage applications are repeated with tampons of the smaller cell size in the same way.

The relief zones of cryo-exposure performed with tampons of different sizes should overlap with no absolutely distinct boundary between them. Continuous “checkered” microfocal real freezing ensures repeated cryo-exposure on the same skin area without risk of blisters appearing after the procedure. A clinical sign of an adequate cryo-exposure is the development of persistent and uniform skin hyperemia. A high-quality cryomassage of face, neck, and décolleté lasts from 40 minutes to 1 hour.

Immediately after completion of the procedure, nourishing and regenerating products in the form of cream or gel should be applied on the hyperemic skin and relevant medications—to the sites of pathological diffuse lesions (acne). Skin cryo-session can be repeated not earlier than in a month.

Currently, cryolifting techniques for the interstitial correction of manifestations of gravitational ptosis on the facial skin by linear subcutaneous cryo-exposure are under development. The outcome of treatment is presented in **Figure 1**.



Figure 1. Facial skin in a female patient (a) before and (b) after cryogenic revitalization.

3. Multiple cryogenic treatment for psoriasis

Psoriasis is a chronic multifactorial systemic disease characterized by epidermal-dermal papular rashes. It occurs with equal frequency in males and females and persists over the years with alternating periods of remission and relapses. It is one of the most common, refractory, and often severe dermatoses. The effective treatment of psoriasis requires considerable efforts but in many cases it comes untenable.

When treating mild forms of psoriasis, dermatologists tend to use the least toxic medications and treatment methods with the lowest risk of possible side effects. If the treatment goals are not achieved, other potentially more effective treatments can be tried but those are more toxic and have a higher risk of serious side effects. Such methods are typically reserved for severe cases resistant to other, less toxic treatment methods for psoriasis. This is referred to as “therapeutic intervention ladder.”

The etiology and pathogenesis of psoriasis is not yet fully identified. Currently, there are two main hypotheses about the nature of the process leading to the development of this disease. According to the first hypothesis, psoriasis is a primary skin disease, when normal processes of maturation and differentiation of skin cells are interrupted and the excessive proliferation of these cells is observed. The defenders of this hypothesis view psoriasis as a disrupted function of the epidermis and its keratinocytes. The second hypothesis assumes that psoriasis represents an immunopathological or autoimmune disease, where the excessive growth and reproduction of skin cells and, particularly, keratinocytes are secondary in regard to various mediators of inflammation, lymphokines, and cytokines produced by the immune cells and/or in relation to the autoimmune damage of skin cells causing the secondary regenerative response.

Genetic determination of psoriasis has never been disputed by medical experts and the extensive clinical experience proves it. Many genes associated with or directly involved in the emergence of psoriasis are discovered but it still remains unclear, how these genes interact in the development of the disease. The majority of genes known to be associated with psoriasis affect the immune system in one way or another, particularly, the function of T lymphocytes and for the major histocompatibility complex (MHC).

So far, the viral theory of the origin of psoriasis is controversial and gives rise to a number of scientific publications, both in favor of this theory, and against it. According to V.I. Kochenov, it is the viral nature of psoriasis, with its patterns of development of clinical manifestations similar to those for papillomavirus that justifies the exclusive adequacy of cryogenic treatment for multiple benign foci of psoriasis.

Indeed, the cryogenic technique allows sparing devitalization of psoriatic lesion, attribute antigenic properties to it, with spontaneous natural phagocytosis, rejection of modified cells and the immunostimulatory effect. At the same time, it provides a possibility of simultaneous radical cryodestruction for the large number of foci on a large area of skin surface without the negative reactions of the entire organism. Moreover, cryogenic treatment stimulates immune activity against the modified cells by performing cryotherapy of the lymphoid pharyngeal ring and the total extreme aerocryotherapy.

The cornified cells in the superficial skin layers form the *stratum corneum*. It is particularly pronounced in the psoriatic lesion and this explains for its considerable elasticity and low thermal conductivity. Special cryoablation techniques are needed for the efficient cryotherapy of psoriatic foci and to stimulate the regeneration of the normal skin cover.

3.1. Cryo-exposure procedure

A full course of successful cryogenic treatment for psoriasis was developed in "OnKolor" Scientific Clinical Center of Medical Cryology. It is important to keep in mind that local cryogenic exposure needed for the complete elimination of the psoriatic focus cannot be referred to as cryotherapy. This should be a proper cryosurgery performed in line with the rules of tumor cryodestruction but less deep penetration of the freezing zone into the pathological tissue.

Therefore, a combination of techniques is applied in cryoablation of psoriatic foci (even if a single focus is treated):

1. Continuous cryo-irrigation with liquid nitrogen until a stable, visible for 5–10 seconds, icing of the entire surface of the psoriatic focus occurs, with two to three iterations of the freeze-thaw cycle at each site during one procedure.
2. Prolonged exposure, with a slow rolling of the cotton wool tampon with braided mesh-like surface chilled in liquid nitrogen on the focus, until a stable, persistent for 4–5 seconds, visible freezing of the psoriatic lesion occurs.
3. Cryoapplication without adhesion performed with passively or actively chilled cryo-instruments by straightening the focal surface and consecutive stops of the applicator for 2–5 seconds at each site.

4. Stepwise freezing of the entire lesion surface by touching with a drop of atmospheric oxygen passively liquefying on the lateral side of the non-thermally insulated cannula and flowing down to “Ledok” cryoapplicator.

It should be noted that in the first two cryodestruction options, psoriatic lesions reveal an increased rate of the surface freezing.

To enhance cryodestruction and increase the cooling rate prior to the cryo-exposure, a mixture of glycerol and dimexidum 40% solution or soft magnetic dosage forms (SMDFs) should be applied to the focal surface and in this case, a permanent magnet is placed around the freezing area.

Thus, one psoriatic lesion is subjected to three freeze-thaw cycles, in line with the above described cryodestruction techniques. Repeated cryo-exposure procedures should be continued until the complete elimination of psoriatic plaques. Complete persistent elimination of dermal psoriatic manifestations can be reached after three to four adequate cryodestruction operations for all psoriatic lesions but may require 5–7 sessions.

The course of general extreme aerocryotherapy (GEACT) included in the cryogenic treatment complex for psoriasis is carried out in “Krion” cryosauna, as follows:

- three procedures per day, simultaneously with the start of the local treatment;
- next, four procedures every other day;
- then one procedure once a week for three weeks; and
- then one procedure per month, up to a year.

Usually GEACT course includes 10–15 sessions.

By the end of a combined treatment course, the remaining minor psoriatic lesions should be impregnated with a mixture of glycerol-dimexidum 40% before the GEACT session. Cryogenic treatment is well tolerated by all patients and has no contraindications.

To enhance the activity of the immune status, local cryodestruction of psoriatic plaques should be supplemented by cryotherapy of the lymphoid pharyngeal ring.

Subject to compliance with these cryogenic treatment recommendations for psoriasis, the patient’s skin stays clean for the period of 1–3 years. However, if there is a slightest tendency to recurrent psoriatic lesion, this site should be immediately subjected to the superficial cryo-ablation. The outcome of treatment is presented in **Figures 2** and **3**.

4. Cryosurgical treatment for warts

Warts are benign skin tumors based on the proliferation of the epidermis and papillary dermis. Warts are caused by the human papillomavirus, which is passed only between humans.

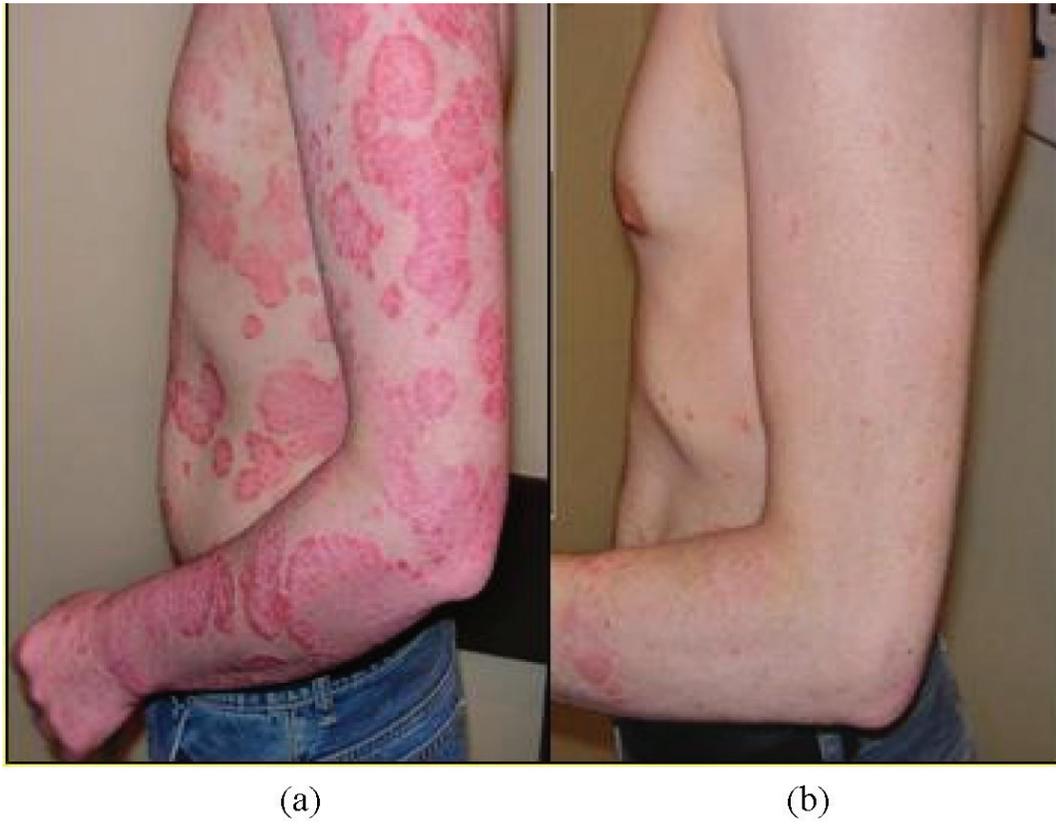


Figure 2. Plaque psoriasis vulgaris: (a) before and (b) after combined cryogenic treatment.

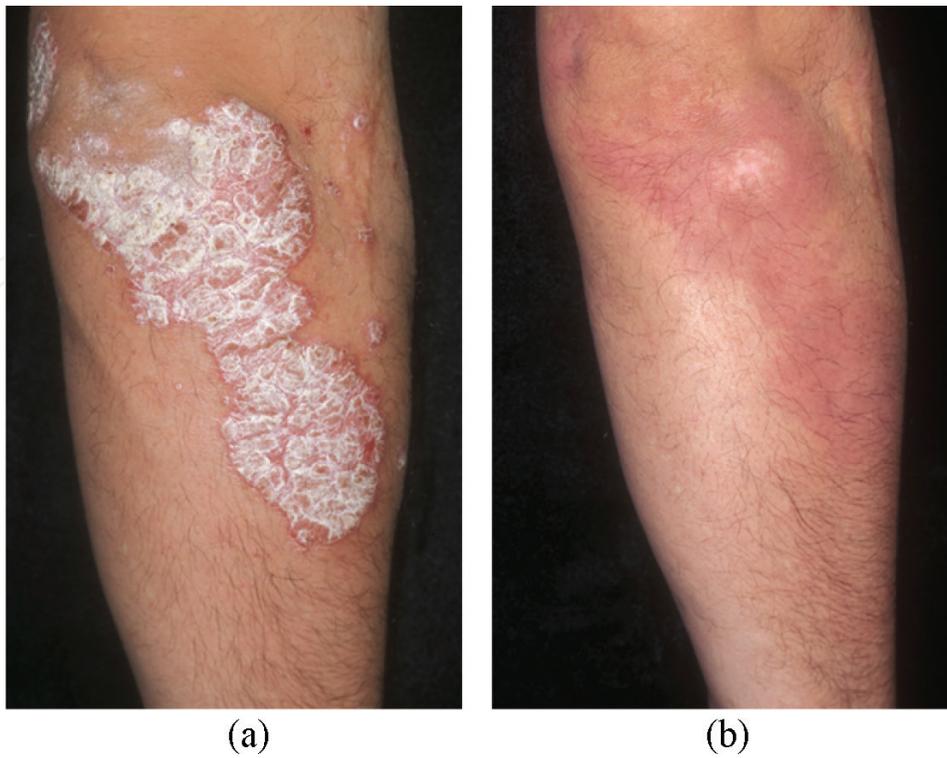


Figure 3. Palmoplantar psoriasis: (a) before and (b) after combined cryogenic treatment.

There are more than 600 HPV strains. According to some estimates, 60% of human population carries this virus.

The following types of warts are distinguished: common, flat, genital, and senile. Common, flat, and genital warts are caused by a single virus. Common warts (*verruca vulgaris*) are the most widespread and contribute to over 70% of the total number of warts. For this reason, we will discuss cryodestruction techniques for this type of warts in detail.

Being the most reliable destruction mechanism damaging all pathological tissues along with preserving cosmetic result, cryosurgery is the best suitable method for the elimination of warts. A very important effect in the treatment of warts by deep freezing is ablastics of cryodestruction that blocks all the elements of the pathological focus and prevents the spread of newly formed wart viruses in the body. They remain in the exfoliated cryonecrotic scab and are removed mechanically from the body.

However, the wart structure is very peculiar, which puts a number of obstacles and complicates cryogenic destruction of this skin formation. Its base goes deep into the tissue and its surface diameter makes always only a portion of the root depth. The wart capsule is dense and dry; the surface is cornified and tuberous, which prevents the proper heat transfer between the cryoapplicator and the pathological tissue.

Thus, the cryoablation technique for the common wart is the same as in the case of a malignant tumor.

Wiping the wart surface with cotton wool soaked in liquid nitrogen does not refer to the radical cryosurgical techniques; such exposure is just too superficial. According to our experience, incomplete cryogenic destruction of wart tissue often stimulates its rapid growth and proliferation.

4.1. Cryo-exposure procedure

First, the wart is prepared by steaming its surface and the *stratum corneum* is removed mechanically to the greatest possible extent. Warts located on the hand back, foot, and the lateral surface of the finger are subjected to cryocompression destruction by capturing with transformation of the affected area into a fold using cryo-clamps with spatial heat accumulators. The exposure time is needed to get the entire surface of the pathological focus and the area of 1–3 mm beyond its borders fully covered by the freezing zone.

This technique is absolutely nonapplicable on the palmar surface and the feet. The basic manipulation for cryodestruction of common warts in these locations is the applicative freezing with adhesion using “Ledok” apparatus. Cryogenic treatment is continued until complete icing of the entire pathologically modified site within its borders.

Icing comes instantly together with the full-rate adhesive effect and freezing-in the working tip into the wart tissue. Therefore, mechanical contact and heat transfer are maintained at all absolute values of the subzero temperature, even after the true adhesive effect disappears. It persists even after the start of passively condensing ambient oxygen flow to the frozen surface via the lateral open surface of the cannula. This phenomenon is used at freezing temperature of -182°C .

The exposure is continued until complete icing of the entire pathologically changed site and the creation of the freezing zone that extends beyond the borders of the skin formation, at a distance equal to its diameter. Only under such excess over the size of freezing zone, the pathological wart tissue is expected to be covered by destructive temperatures.

Freeze-thaw cycles for each wart are repeated three times, regardless of the cryoablation technique.

Another option for additional deep local cooling, appropriate for large-size common warts, is cryo-irrigation of the wart surface with the same parameters of freezing expansion area, which is carried out at the final stage. Cryo-irrigation as a single freezing method cannot be recommended for eliminating warts.

Genital warts, flat warts, and senile warts are subjected to cryo-compression destruction as described above, by using a cryo-instrument with spatial heat accumulators of the most appropriate size.

5. Cryosurgical treatment for purulent diseases of the skin and subcutaneous fat using SMDF in a magnetic field

Purulent diseases of the skin and subcutaneous fat account for about 70% cases in surgeon's outpatient reception. The most common causative agent of these diseases is the staphylococcal flora (70–90%).

The main purulent diseases of the skin and subcutaneous tissue include furuncle, carbuncle, hydradenitis, and abscess. Diseases complicated by lymphangitis and lymphadenitis take a particularly severe course. In addition to surgery, treatments of purulent diseases of the skin and subcutaneous fat use an intensive combined treatment: antibacterial, detoxification, and immunomodulation.

Following the rejection of a rod consisting of necrotic tissue and pus, ulcer-like skin defect is formed, is rapidly replaced with granulation tissue and healed by secondary intention, leaving a deep inverted scar. A cosmetic skin defect is often formed at the site of surgical wound.

In recent decades, active development of cryosurgery attracts particular attention, due to the creation of uncomplicated, reliable, and inexpensive cryogenic devices. An important factor is the elimination of the causative agent of purulent infection in the inflammation focus subjected to freezing, with subsequent fixation of purulent focus by swelling of the underlying tissues and vascular thrombosis.

Currently, the cryogenic treatment for purulent diseases of the skin and subcutaneous fat is almost unused, despite its proven success, as described in some published works.

Obviously, difficulties arise during freezing pathological cavities. This situation can be addressed by the creation of heat-conducting liquid layer between the cryoapplicator tip and the freezing tissue, providing adhesion and congruence of surfaces. Traditional use of aqueous

layers, which are characterized by low thermal conductivity, impairs the main characteristics of the cryo-instrument, while oil- and alcohol-based layers have even lower heat conductivity and adhesion capacity.

Furthermore, healing under cryonecrotized biological tissue occurs in two main stages. First, necrotic tissue is transformed into long-drying moist cryonecrosis. Due to the fact that cell membranes are damaged by ice crystals formed during freezing, the intracellular fluid exudes to the surface of cryonecrotic tissue, thus preventing the secondary infection of cryonecrosis. When the exudative process concludes, moist cryonecrosis turns into a solid dry scab—dry cryonecrosis. During this period, the epidermal cells regenerate from the periphery to the center. The time length of regeneration correlates with the focal diameter of the cryogenic lesion and its depth. During this period, the dry cryonecrosis covers the wound surface and acts as an antiseptic dressing.

Since the dry cryonecrosis has a much lower elasticity, as compared to the skin, it tears away during the healing process. This process is promoted by the natural partial exfoliation of dry cryonecrosis from the periphery as regeneration proceeds.

If purulent diseases of the skin and subcutaneous fat are subjected to superficial cryo-exposure, microbial associations are often preserved in the pathological cavity. To avoid this situation, cryodestruction should be performed more intensively. An increase in the depth and area of cryo-exposure will inevitably result in a more extensive damage to healthy tissues and will significantly lengthen their recovery.

Such problems as an insufficient depth of cryo-exposure or a significant surface expansion of the freezing zone on healthy tissues in an attempt to increase the depth of the freezing area, the lack of effective heat transfer and the duration of postoperative period remain yet unresolved and restrict the application of the cryogenic method in the treatment of purulent diseases of the skin and subcutaneous fat.

A new class of pharmaceuticals that appeared in recent years includes preparations that have high thermal conductivity and are capable of penetrating into small cracks, pores, caverns, ducts, and various cavities in the presence of magnetic field, which enables a wider use of the advantages provided by the cryosurgical treatment.

SMDF is a pharmaceutical form containing fine particles of magnetized ferromagnetic (Fe_2O_3 – Fe_3O_4 , $\text{SrO}\cdot 6\text{Fe}_2\text{O}_3$, Nd-Fe-B , FeB). SMDF consistency, viscosity, and fluidity depend on concentrations of ferromagnetic and the base substance. As the strength of magnetic field increases, SMDF thermal conductivity approaches that of the metal, i.e., SMDF is in fact a soft metal body. It comes important with regard to the fact that thermal conductivity increases in cryo-exposed pathological tissue and subsequently, the destructive effect of cryoablation is enhanced.

Moreover, SMDF applied locally has pronounced antiseptic and dehydrating effects, which are essential in the postoperative period to reduce the moist necrosis phase and accelerate the regeneration under dry cryonecrosis. These effects can be supplemented, if necessary, by the introduction of anesthetic, hemostatic, vasoconstrictive and other medications into the SMDF composition.

5.1. Cryo-exposure procedure

Cryosurgical treatment of patients with purulent diseases of skin and subcutaneous fat does not include the general antibacterial therapy.

Antibacterial agents are applied only locally in ointment. To enhance skin susceptibility to penetration of all SMDF components, dimexidum (dimethyl sulfoxide, 40% solution) is included in the ointment composition.

During the *infiltration stage*, SMDF is applied to the entire zone of hyperemia, the cryoapplicator is brought into contact with the magnetic ointment, and cooling is performed until the freezing zone is spread to the uninflamed skin. Under such short-term cryo-exposure, superficial cryonecrosis is formed, not deeper than 1.2 mm (**Figure 4**).

A sharp pain in the inflammation focus perceived by patients prior to the cryo-exposure therapy is arrested. Edema and hyperemia of the infiltrate that develop within hours after cryoablation disappear in the first 2–3 days. Necrotic tissue has an intense dark brown color, due to the admixture of ferromagnetic particles.

In the postoperative period, magnetic ointment should be replaced daily, simultaneously by applying magnetic fields to the focus of inflammation. The thin cryonecrotic layer is rejected within 7–10 days, depending on the area of cryonecrotized tissue.

During the *necrosis stage*, cryo-exposure is performed until the freezing zone is spread on the healthy tissue, then the edema of subcutaneous fat in the entire depth of the abscess is developed in 20–30 minutes. When swelling is observed below the focus of purulent inflammation, the pyogenic abscess is dissected. Pus and necrotic content are removed from the furuncle cavity by washing with 0.9% isotonic solution. Then, SMDF is injected in the abscess cavity with a syringe.

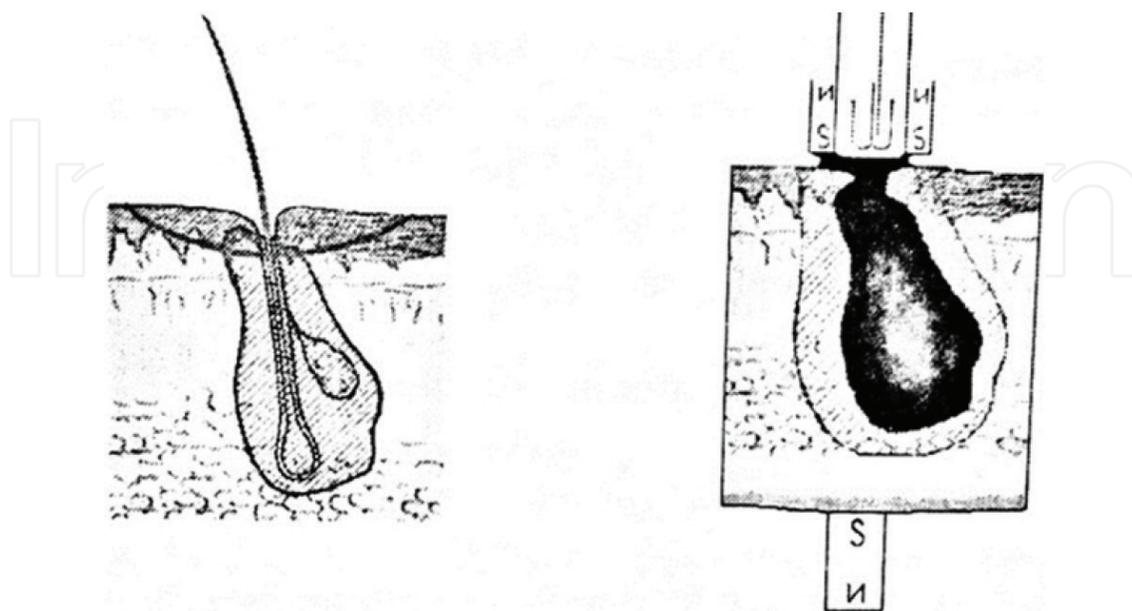


Figure 4. Spread of the freezing zone produced by the traditional cryoablation and by SMDF in a magnetic field.

Magnetic fields generated by the permanent magnets promote the maximum penetration of the ointment into the abscessed cavity. A cryoapplicator is brought into contact with a ferromagnetic ointment on the abscess surface and it starts cooling. Thus, the cavity is frozen inside by using SMDF as a thermally conductive material. At the same time, the effect of magnetic field should not be interrupted, in order to enhance thermal conductivity of the ointment.

In the postoperative period, most ointment is removed spontaneously together with the exudate. The ointment residues are removed from the abscess cavity with a cotton tampon and a permanent magnet, and then fresh ointment is introduced with a syringe. During the wound healing, ointment containing the antibacterial agent should be applied on the surface of the cryonecrotic tissue. As regeneration goes, the wound healing occurs by the day 7–10, without scar formation.

In the *open abscess stage*, the cavity is flushed with 0.9% aqueous solution of sodium chloride to evacuate necrotic masses, with the subsequent cavity filling by SMDF, performing cryo-exposure and maintaining the postoperative period in line with the above described procedure.

The experience of magnetic ointment applications proved that SMDF allows for establishing a tighter thermal contact between the cryo-instrument and the tissue, to accelerate cooling and increase its depth, due to higher thermal conductivity of SMDF, and to intensify frost penetration into the deep tissue, due to the active SMDF penetration into the pathological substrate.

Applying additional SMDF on the abscess surface in the postoperative period reduces the periods of moist and dry cryonecrosis, due to the stimulation of regenerative processes.

The postoperative use of magnetic ointment makes possible exclusion of systemic antibiotic therapy, eliminates formation of cosmetic defects on the skin and prevents the development of complications.

It is particularly important that the cryosurgical method using SMDF provides absolute elimination of pyogenic bacteria, particularly, methicillin-resistant *Staphylococcus aureus* (MRSA) resistant to traditional methods of antibacterial treatment.

6. Cryosurgical treatment for epithelial cysts

Epithelial cyst is a cavitory lesion developed from the epidermis; its capsule produces the mass filling of the cyst. Epithelial cysts of the skin are classified into several types depending on their microscopic structure: epithelial (epidermal), dermoid, and trichilemmal cysts.

Epithelial cysts are traditionally treated with surgical methods. Cystectomy implies the excision of the entire cyst capsule together with the intact surrounding tissue through cuts outside of the cyst. Under pyogenesis, the cyst is first subjected to oncotomy only and cystectomy is performed when inflammation decreases. This treatment leads to a cosmetic defect in the form of scar and pyogenesis poses another problem—completeness of the capsule removal, when its remains to create conditions for disease recurrence.

Cryosurgical treatment for epithelial cysts eliminates the occurrence of relapse and improves cosmetic result of the operation. A set of instruments for medical cryology suggested by Dr. V.I. Kochenov is intended for the efficient implementation of various techniques of deep local cryoablation of various cysts localized visually. Instruments and methods should be used differentially at different stages of the operation depending on the cyst size and its location/depth.

6.1. Cryo-exposure procedure

Prior to the start of cryo-exposure, the surgical field is treated with antiseptic and the skin is irrigated with 10% lidocaine solution.

For *cysts of less 8 mm in diameter*, with their content visible through the skin or mucosa, cryo-compression destruction is performed by capturing pathological tissue in the fold with cryo-grasp accumulators cooled passively in liquid nitrogen. After the first freeze cycle, the cyst cavity is perforated by a pointed cryostick cooled in liquid nitrogen during spontaneous thawing phase. In the next cryocompression freeze cycle, the cyst content should be evacuated by bringing together cryoaccumulators to the closest possible position. Thus, two freeze-thaw cycles are performed under tight pressing of collapsed cyst walls to each other and with the time of cryo-exposure equal to 3–5 seconds.

For *cysts of up to 1.5 cm in diameter* and transparent contents, cryodestruction with adhesion is performed with “Ledok” cryodevice with active supply of liquid nitrogen. The exposure is continued until the freezing zone extends 1–2 mm beyond the projection of the cyst diameter from all sides. During spontaneous thawing and some softening, a linear incision, 4–6 mm long, is performed with a scalpel, with penetration into the cyst cavity and its content is removed with a Volkmann spoon. Then a warm rounded applicator sized to the diameter of the cyst cavity is inserted through the produced hole, as if the cystic bag is put on the cryo-applicator. The operation is carried out in two to three freeze-thaw cycles, cryo-exposed for 5–10 seconds and under palpation control.

For *cysts of up to 1.5 cm in diameter* and nontransparent content, cryo-exposure is performed through applications with active cryoapplicator adhesion or by pulse cryo-irrigation onto the projection of the cyst center with 2–3 mm extension of the freeze zone beyond its borders. Without waiting for complete thawing, incision is made with a warmed scalpel (or focused radiation CO₂ of laser/RF scalpel) in the projected cyst center with penetration into the cavity, in order to evacuate its content during the thawing phase. In the process of thawing, the cyst is emptied and then dried. Next goes cryo-insufflation of the cavity using the cryo-spray device. Cryodestruction is completed by cryocompression freezing under tight pressing of the collapsed cyst walls. The exposure is continued until the freezing zone is established at 2–3 mm beyond the cyst borders.

For *cysts with a thin capsule* and provided that the rounded cyst shape is not regained after compression, the operation is finalized at this stage and pressure dressing is applied.

For *cysts with a dense capsule*, multidirectional cryo-irrigation is carried out within the cystic cavity prior to its icing. After thawing, a warm cryoapplicator with a protective insulating

element with axial displacement is introduced into the cyst cavity. The free distal tip of the applicator is placed into contact with the cavity bottom and liquid nitrogen is applied briefly until adhesion appears. Then traction is performed with a cooled cryoapplicator in rotational clockwise motion, thus reaching full excision of the epithelial cyst capsule, and the operation is completed.

In the presence of inflammation or purulence, the cyst is dissected with a cryo stick chilled in liquid nitrogen, its content is evacuated, the cavity is washed with chlorhexidine 0.05% aqueous solution and dried. Then, a warmed "Ledok" cryoapplicator of the appropriate size and with active supply of liquid nitrogen is inserted into the cyst cavity and the cystic capsule is subjected to cryodestruction with adhesion, performing three freeze-thaw cycles, with an exposure time of 5–10 seconds and under palpation control.

When the cavity diameter is larger than the cryoapplicator, it is filled with the soft ferromagnetic heat-conducting ointment or gel (a 20% mixture of nano-ferromagnetic particles of carbon iron in antiseptic ointment or gel base) and then the applicator is dipped into it. A ring-shaped permanent magnet should be placed around the cyst projection. Freezing with adhesion is carried out until the freezing zone is spread 2–3 mm beyond the cyst capsule in all directions, in three freeze-thaw cycles.

When the cyst cavity diameter is much larger than the applicator, it should be moved with pressing to different sites of the walls until icing, in order to ensure at least triple freezing of each site of the cyst capsule and surrounding soft tissues.

Cryosurgical treatment for epithelial cysts allows to:

- guide surgical interventions directly onto the cyst projection and into its cavity, rather than around it, thus reducing the width of the surgical field and the incision;
- ensure radical treatment through the absolute destruction or complete and quality removal of the entire capsule;
- eliminate the cause of recurrence;
- perform cryo-exposure in a differentiated mode depending on the size, depth of the cyst location, as well as the capsule thickness;
- provide ice fixation of the cyst capsule at the moment of its dissection;
- prevent formation of a scar and cosmetic defects; and
- achieve the absolute elimination of pathogenic flora under inflammation and purulent dissolution of the cyst content, simultaneously with its removal.

Thus, cryosurgical treatment for epithelial cysts is acceptable both in non-inflammatory and purulent conditions. A thin cyst capsule is easily subjected to the total cryoablation, whereas thick capsules of larger cysts are better treated by cryo-excision. This technique allows for a radical treatment, which excludes relapse in the long term. In addition, cryosurgical treatment of epithelial cysts provides a good cosmetic effect. In the course of the epithelial recovery, the cryo-necrotic scab is rejected gradually layer-by-layer, without scarring.

7. Cryosurgical treatment for skin hemangiomas

Hemangioma is the most common benign tumor formed by blood vessels. This tumor develops, due to the unrestrained growth of defective blood vessels, which are arranged randomly, fail to perform blood circulation in tissues and organs, and form a tumor [1, 2].

The results of various treatments for skin hemangiomas are not always satisfactory for the patients and doctors. Relapses and cosmetic defects are observed commonly after the treatment.

Application of cryogenic treatment to skin hemangiomas was limited by the lack of adequate cryo-instruments needed for the effective cryoablation. The available cryogenic equipment was used in the treatment for extensive large hemangiomas located in the parenchymal organs, whereas there were no targeted developments for the treatment of cutaneous hemangiomas. Previously, application techniques were widely used for this purpose. However, recent developments made a step forward to the use of cryosurgical methods for treating skin hemangiomas of any localization and of different sizes.

The instrument, which proved the most optimal in cryosurgery of hemangiomas, was manufactured by the order of Cryology laboratory, Department of operative surgery and topographic anatomy, Nizhny Novgorod State Medical Academy, and was included in the Medical Cryology Set proposed by Dr. V.I. Kochenov [3].

The instrument is made of a metal alloy with high heat capacity allowed to be passively cooled in liquid nitrogen. It comprises movably connected jaws with ring-shaped handles; their working parts, from the place of joint to the distal tip, are made spatial, with the possibility of closing the working surfaces relative to each other. When closing, the outer surfaces of the jaws' working parts are oval-shaped; the distal tip is sharpened at an angle of 30–35° to the closing plane; the length of each is 30 mm (can range up to 40 mm). The greatest convex extension of jaws corresponds to the middle of the oval and makes $\frac{1}{5}$ of its length. Capillary slit-like grooves for penetration of liquid nitrogen are made in the deep working part of jaws and are directed to its distal parts. All instrument surfaces are polished.

7.1. Cryo-exposure procedure

When performing cryoablation, the internal surfaces of working parts of jaws act as applicators and the exophytic part of hemangioma is clamped between them. If the hemangioma is flat, i.e., is located deep in the skin, it is captured in a skin fold, so that the entire formation is fixed between the jaws and the slit grooves are directed up and down. Liquid nitrogen flows via grooves to the hemangioma and enhances freezing. When performing cryo-exposure, the hemangioma is compressed by $\frac{1}{2}$ – $\frac{1}{3}$ of its diameter; then, it is slightly retracted and rotated to an angle of up to 45° to the skin surface. When the freezing zone is expanded to 5 mm beyond the perimeter of the tumor base, the contact is ceased and the instrument is removed. After complete spontaneous thawing of the hemangiomas, all manipulations are repeated thrice in the same order. After freezing of the hemangioma tissue, cryobiopsy for histological examination should be taken.



Figure 5. Hemangioma on the breast skin: (a) before and (b) after cryodestruction.

The time of cryo-exposure to liquid nitrogen may be different in each case; the average value is 60 seconds. All capillary skin hemangiomas of any location, sized up to 3 cm², regardless of their number, are recommended to cryo-exposure in a single session.

The advantages of cryosurgical treatment for hemangiomas are as follows:

- wide range of indications (no restrictions on age, number, location, size, and morphological type of hemangiomas);
- no limitations on the volume and number of hemangiomas subjected to simultaneous cryo-ablation; and
- good cosmetic results after treatment (rehabilitation of the normal skin color and structure without scarring and depigmentation). The outcome of treatment is presented in **Figure 5**.

8. Cryosurgical treatment for precancerous skin lesions

The term “precancer” was introduced by the French dermatology researcher N. Dubreuilh over a hundred years ago. This term denotes the processes that precede the development of a malignant tumor but not always result in cancer formation. Further in 1933, S.C. Becks suggested the division of precancerous conditions into the obligate and facultative.

Under obligate precancerous diseases, skin changes are characterized by the oppositional type of growth and their reverse development is not observed. In the current world literature, local malignant processes that do not spread beyond the skin cover are described commonly as carcinoma *in situ*.

Under facultative precancerous conditions, cornification of the mucous membrane and stromal inflammation are observed. The greatest significance in the genesis is attributed to the cell hyperplasia, which differs from regeneration by the fact that it goes beyond the physiological needs and transforms into dysplasia. Dysplasia has three stages—strong, medium, and weak; of those, the first represents a reversible process already with some signs of morphological anaplasia, the second comes close to a tumor, and the third sometimes cannot be distinguished from it. All these clinical signs should raise cancer alertness.

According to WHO experts, the recent and predicted increase in the incidence of malignant skin tumors is explained by the characteristics of the skin being the most exposed to unfavorable exogenous factors organ. The foci of superficial dyskeratosis very often contain human papillomavirus of strains HVP-16, HVP-31-35, HVP-51-54, and others. Histological examinations of precancerous skin lesions reveal inflammatory and hyperplastic processes.

The number of skin and mucosal tumors increases with high malignant potential and this confirms the current need in methodological improvements in early detection technologies, timely and adequate treatment of patients with visually localized tumors with a high tendency toward malignant transformation.

In this context, such advantages of cryosurgery as affordability, effectiveness, minimal invasiveness, possibility of geriatric application, ablastics, organotypic regeneration, as well as triggering the general immune-stimulating antitumor effect by preserving nativity of pathological protein and nucleic acid structures of the rejected tumor are particularly important.

Unlike the most common minimally invasive treatment techniques—electrocoagulation and laser destruction—cryoablation features the delayed necrosis development, which allows obtaining a section of the frozen, i.e., non-viable tissue suitable for morphological examination.

The antitumor immunostimulatory effect is triggered against the neoplasm subjected to cryoablation and preserved at the time of cryonecrosis formation. According to Dr. V.I. Kochenov, the effective induction of specific antitumor immunity is achieved by introducing a natural immune stimulation into the mechanisms of the general therapeutic and prophylactic antitumor effect during cryoablation.

However, cryoablation is often applied to neoplasms diagnosed by inspection only, without morphological examination. This situation complicates the problem of their quality treatment. In dermatology, morphological examination plays an important role in dyskeratosis diagnostics, whereas cancer diagnosis lacking morphological verification is considered nonvalid.

Special attention should be paid to the eczema-like skin lesions accompanied by itching, burning and pain, unevenly colored spots with scaling phenomena, focal plaques with moist velvety surface and areas of hyper- and hypopigmentation, focal changes with erosions, ulcerations and nodules, plaques covered with dry rough scales resembling psoriatic plaques, focal skin lesions with blurred contours, and a tendency to peripheral growth. Such focal transformations of the skin should never be subjected to an intervention without morphological diagnosis and they require radical treatment. Histological examination of these tissue fragments should be conducted after preliminary cryoablation.

The quality of histological examination, clinical and histological diagnoses, as well as selection of further treatment and the overall cosmetic result depend on a properly performed biopsy. However, the potential of morphological diagnosis for cryology is underutilized by dermatologists and cosmetologists. To solve this problem, cryodestruction should be combined with biopsy that would improve significantly the quality of diagnostics and treatment of precancerous skin conditions.

The temperature regimes of cryoablation are not yet standardized; the applicator's temperature ranges from -60 to -180°C in different devices, which affects the cryoablation quality and prevents comparing cryoablation results obtained for similar pathological changes by different authors. In some cases, treatment of precancerous skin conditions is attempted by applying cotton wool soaked in liquid nitrogen, despite the fact that this technique is inapplicable even for superficial therapeutic cryo-exposures, since the temperature in the contact zone (cotton-pathological tissue) does not fall below -20°C . Therefore, in cryosurgery of precancerous skin diseases, we need to find a way for standardization, in regard to the intensive destructive effect and visualization of the lowest temperature of cryoapplicator used for tumor destruction.

Another unresolved cryoablation problem is how to determine the completeness of cryo-destructive effect at early stages. Today, the completeness of cryo-destructive effect is most often determined visually by the presence of a tumor residue, 1–1.5 months after the full cryonecrosis rejection, which is absolutely unacceptable in case of malignant neoplasia. During the period of cryonecrosis rejection, the tumor can grow significantly and even spread metastases.

The current recommendation in cryosurgery is to achieve the expansion of the freezing zone 2.5 cm outside the visible tumor borders is only a safety net when the cryoapplicator in use has an insufficiently low temperature and contains no objective productivity criteria for cryo-destruction in any pathological focus. There are no available literature references about the early criteria for localization of the prospected cryonecrosis rejection line to be defined morphologically in the first days after cryodestruction.

To address these objectives and in order to improve the quality of treatment for precancerous skin diseases, the major conditions should be implemented:

- to develop visualized standardization for the intensity of cryogenic destruction of the pathological tissue; and
- to ensure monitoring of early adequacy of cryodestruction volume for various tumors, along with defining the projected borders of the deep cryonecrosis zone.

These objectives are achieved through the following steps. Cryoablation is performed in at least two freeze-thaw cycles with adhesion and cover all clinically defined tumor volume by the freezing zone. The working part of the instrument should be cooled to below -182°C , as can be evidenced by visible liquefaction of atmospheric oxygen fraction. The next step is excision of the pathological tissue for morphological examination within 6–12 hours after cryoablation. The fragment is removed with a warmed scalpel (or CO_2 laser, RF-scalpel) via oval cuts in the direction of possible infiltrative growth. The cut is made in a single block that includes the frozen tumor tissue and non-frozen ambient healthy tissues surrounding the freezing zone.

After that, local freezing for hemostasis is performed in the defected area of the tumor bed and then a series of column biopsies is carried out along the tumor radius line, in the direction of the most probable latent growth, with access to the clinically healthy tissue in depth and to the periphery.

Histological examination of the excised tissue fragments and in a series of column biopsies involves morphological identification of tumors and comparison between the boundary of pathological changes and the boundary of small blood vessels thrombosis on the surface and in depth. If the zone of pathological changes does not extend beyond the borders of thrombosis, the cryogenic destruction of a tumor is considered complete, otherwise additional, deeper and broader cryodestruction is performed and cryo-extirpation is applied to the transformed site. Additional cryodestruction is carried out in such a way that the freezing zone overlaps the borders of pathological changes identified by histological examination.

In 6–12 hours after additional cryodestruction, the tissue fragments are excised for repeated morphological examination using the same methodology as earlier. Then a series of biopsies is taken along the radius line of the tumor in the direction of the latent growth detected histologically, with access to clinically healthy tissues. After removing the column tissue fragment and if hemostasis is needed, cryo-exposure is performed inside the channel by cryo-insufflation or by inserting the cryoapplicator of appropriate diameter into the channel.

When the pathologically changed tissues are absent beyond the borders of thrombosis, cryodestruction is considered as radically complete. In the postoperative period, antiseptic care for the cryonecrosis zone is carried out until its rejection.

According to physics studies, the temperature of liquid oxygen is -182°C . The phenomenon of ambient oxygen liquefaction on metal objects cooled with liquid nitrogen occurs due to the difference between the temperature of liquid nitrogen (-196°C) and the temperature of oxygen liquefaction at normal atmospheric pressure. Physical and chemical experiments demonstrated that the atmospheric fraction liquefied passively with the most chilled instruments represents molecular oxygen.

The optimal time for histological sampling was identified by the experimental studies on animals with grafted skin tumors. It turned out that the minimum period for the emerging first signs of localization of the future demarcation line is 6 hours, and this sign is a line of ingression of solid thromboses in all blood vessels in the tissue. 12 hours is a period when necrotic changes do not complicate morphological identification of the tumor after cryoablation.

Moreover, the experiment shows that a clearly established border of the future cryonecrosis and tissue rejection at the border of solid thromboses occurs within the specified time period only after the most intensive applicative cryodestruction performed with adhesion and against the temperature of cryoapplicator, which visualizes the ambient oxygen liquefaction on the cryo-instrument. Cryodestruction performed at less values of negative temperatures does not provide a clear boundary for the future demarcation line in 6 hours and the cryonecrosis border does not coincide with the boundary lines for thromboses and freezing but lies within this zone, because cryoablation process at temperatures less than -182°C proves less effective.

The proposed cryosurgical method of treatment ensures the following positive effects:

- radical therapeutic effect for all precancerous diseases of visual localization;
- standardization of the most intensive destructive effect from cryoablation, due to the stabilization of the lowest temperature value for cryoapplicator;

- visualization of the lowest possible temperature on the cryo-instrument, under ambient conditions;
- emergence of a stable, well-defined under visual and histological examinations, change in the tissues, which coincides with the line of the future tissue rejection—solid thrombosis of small blood vessels that appears in a clearly defined time frame and depends on the intensity of cryoablation;
- simultaneously provided morphological verification of the diagnosis of skin tumor to be removed and the evaluation of radicality of cryogenic destruction;
- possibility to confirm the completeness of the destructive effect underway within the first day after cryoablation and to identify the need for additional cryogenic exposure;
- ensuring the absence of relapses, even in malignant tumors at early stages;
- robust hemostasis during manipulations; and
- histotypic tissue regeneration, without the formation of rough scar.

9. Cryo-circular excision in treatment of skin melanoma

Along with squamous cell and basal cell skin cancers, melanoma refers to the malignant tumors and represents one of the most dangerous skin cancers in humans, which is often recurrent and metastasizing into almost all organs via lymphatic and hematogenous pathways. Its characteristic feature is a weak or even absent response of the body, so melanoma often progresses rapidly [4–6].

In the opinion of medical cryology community of Nizhny Novgorod, the major advantages of cryosurgery are best manifested in treating the skin melanoma, such as ablastics, due to the tissue reactions that develop immediately after freezing (swelling around the focus with an increase in the interstitial pressure, lymphostasis, compression, and thrombosis of blood vessels), and feasibility of application in hard-to-reach areas of tumor location. Studies conducted by the national and foreign researchers have proved that cryogenic exposure creates conditions for rapid fixation of melanoma cells with their subsequent devitalization and thus can prevent the dissemination of tumor cells as much as possible [3, 7, 8]. The cryogenic method is a choice of priority in treating skin melanomas located in anatomically inaccessible places, such as the external ear, angle of eye, nose wing, etc., where traditional surgical intervention is associated with the formation of a cosmetic defect.

Diagnosing melanoma is distinguished by an absolute ban on aspiration, incisional or excisional biopsy. Such intervention gives an impetus to the intensive tumor growth, metastasizing, and hematogenous dissemination of the process [8–10]. In regard to melanoma, only complete removal within the healthy tissue is permissible, with subsequent histological examination. In all cases of the emerging pigmented skin tumor or rapidly changing pigmented formation against the absent clinical signs of cutaneous metastasis, diagnosis and treatment

should be started with the cryogenic exposure. During this procedure, a column biopsy is taken and a part of pathological tissue is forwarded for complete morphological examination. Sampling for histological examination should include two tumor fragments—for urgent and routine examination. Such approach ensures the absolute ablaticity and high diagnostic accuracy, despite the conventional view that cryodestruction of melanoma is not applied, due to the impossibility to reliably determine the level of invasion into the underlying tissues [11].

One of the reasons for the unsuccessful radical cryodestruction of malignant tumors is the inclination to visually correlate the clearly defined (usually, ultrasonic-aided) freezing zone with a hypothetical tumor boundary. However, malignant tumors are distinguished from the benign ones by lacking clear boundaries. Variable prediction of tumor infiltrate boundaries is possible only at early stages, and they are highly individual for each type of a malignant tumor and its localization, which stipulates the urgent search for the boundaries of the latent spread of the primary focus of neoplasia. The computerized microdermoscopy systems available to date improve early melanoma diagnosis from 60 to 90%, but often under experimental conditions only. Therefore, if cryodestruction is applied solely with a radical purpose, even with localized, externally small malignant tumors, it should be performed within the frame of generally accepted rules of surgical radicality.

No less surprising is the faulty trend to issue indications for cryodestruction only after unsuccessful treatment outcomes from all other methods or during relapses. Obviously, combining radio- and chemotherapy technologies with cryodestruction are expedient in conditions of the disseminated process. Such combination has logic and sense when planning deep freezing of the entire neoplasm prior to radiotherapy, regional or systemic chemotherapy, since under this condition, cryodestruction brings the effect of potentiation and initially provides ablaticity to the whole treatment schedule.

A string requirement in applying the cryogenic method is the availability of appropriate cryo-applicators capable of creating complete and irreversible necrosis of the entire volume of tumor tissue within the surrounding healthy ones [3].

9.1. Cryo-exposure procedure

The most adequate instrument for deep freezing of the skin melanomas is an applicator with a ring-shaped working surface and an open tube mounted on it. The applicator is placed on the healthy tissue around the tumor. Cryodestruction is performed with a continuously cooled ring-shaped cryoapplicator until the freezing zone expands 1–2 mm beyond its boundaries. Deep cooling with adhesion allows for freezing melanoma with simultaneous and all-round preblocking of blood supply, which excludes mechanical contact with the tumor. The tube accelerates the freezing process, due to the simultaneous direct exposure of the exophytic part of the neoplasm to liquid nitrogen. Cryobiopsy is taken via the tube opening without breaking contact between the instrument and the frozen tissue.

When the diagnosis of skin melanoma is confirmed by the urgent histological test, cryolaser excision of the tumor is performed in a single frozen block. Focused radiation of the CO₂ laser is directed along the frozen tissue surrounding the applicator, preferably around –20°C

isotherm. Additional cryo-irrigation along the incision line is carried out using “Ledok” apparatus. Such excision may also be performed using ЭХБЧ-500 electrosurgical apparatus (electrocautery). The control biopsy is taken from the sides and the bottom of the resultant wound defect, as well as around its circumference, stepping 0.5–2.5 cm from all sides (depending on the tumor thickness). The postoperative wound is closed in layers.

Application of this technique in patients with skin melanoma (operated using tumor cryofixation, cryobiopsy, and cryo-extirpation) can reduce significantly (twofold to threefold) the volume of surrounding healthy tissues removed during surgery, as compared with the traditional surgery. Another advantage of this technique is the fact that preradiation therapy is not required. When used properly, this technique demonstrates 100% 5-year survival rate of patients.

If the absence of metastases is confirmed, cryoablation may be applied without removing a single block of the frozen pathological tissue, in order to provide the immunostimulatory effect by prolonged preservation of the devitalized frozen tumor tissue in contact with the body. In such cases, a ring-shaped applicator or “Ledok” cryoapparatus (with nonvacuum cannula of 10–12 mm diameter, opened at the working end) are used.

To enhance heat transfer and encapsulation properties, magnetic gel is used in cryo-circular excision, applied as a sealing layer to the healthy skin at the site of the expected cryoapplicator placement and a ring-shaped magnet placed at the applicator. Radical cryoablation for the skin melanoma is performed in five to seven freeze-thaw cycles depending on the size of neoplasia.

When implementing cryoablation with “Ledok” device, a cotton ring impregnated with dimexidum 40% solution should be tightly placed around the applicator at the distal part of the cannula. This ring provides adhesion and, being passively soaked by the liquefied ambient oxygen flowing down along the cannula wall, represents an active cryoapplicator continuation when its temperature is stabilized at below -182°C , and surrounds gently the tumor tissue of any configuration.

At the first stage, the tumor is frozen up to its visible borders; then the cannula is warmed actively and retracted. After that, cryobiopsy is taken via a hole in the frozen cotton ring. Urgent morphological confirmation of the melanoma diagnosis qualifies for the extensive cryosurgery, upon the same methodology, providing a visible spread of the freezing zone beyond the tumor border not less than 1.5 cm in all directions, overlapped freezing zones and five to seven freeze-thaw cycles repeated for each point of the visible pathological tissue.

All manifestations of facultative precancerous skin diseases (in particular, all exophytic pigmented lesions) are subjected to cryoablation in the same or the next day.

At the stage of clearly marked demarcation line and gradual dehydration of the top cryonecrosis layer (3–5–7 days after the first cryoablation), cryo-destruction procedure is repeated, in order to accelerate mummification of the pathological tissue. It is preceded by the removal of exophytic part of cryonecrosis and repeated column cryobiopsy, multiple by the tumor radius, 1.0 cm indented from the primary focus to underlying healthy tissues (the first underlying fascia) is taken.

If foci of neoplasia are detected, additional cryodestruction of the tumor bed should be performed by the method of interstitial linear freezing with needle flow applicators or the cryolaser destruction is applied.

To evaluate the immunostimulatory therapeutic effect, we have examined the immunological status before and after treatment, once in every 2 months during the first year and once in every 3 months for 5 years starting from the second year. Humoral and cellular immunity was evaluated using monoclonal antibodies $CD_{3'}$, $CD_{16'}$, $CD_{4'}$, $CD_{8'}$, CD_{4}/CD_{8} .

Application of cryosurgical treatment for skin melanoma was accompanied by twofold increase of CD_{4}/CD_{8} , as compared with the baseline value; in 6 months, the CD_{4}/CD_{8} level averaged 1.5 ± 0.2 . Thus, the cryosurgical treatment provides an immunostimulating effect, while the consolidating effect lasts approximately 48 months, depending on the reactivity of the immune system.

It should be particularly noted that the mummified cryonecrosis sites on the skin larger than 4–5 cm² require active mechanical removal within 1–1.5 months after cryoablation, otherwise the epithelialization process is delayed and the dried cryonecrosis site displays itself as a foreign body, thus becoming an activator of the secondary inflammation. Complete rejection of the damaged melanoma tissue occurs within 2–3 months.

Filling the defect with local tissues or a displaced skin flap after cryo-circular excision of skin melanoma is not required. The retracted scar can remain in the cryoablation zone but it is incomparably smaller and has less cosmetic defect than that after traditional surgical excision of such tumor. Local recurrence is not observed provided that all requirements for this technique are met.

Specific features of the cryo-circular excision method for skin melanoma make it advantageous for outpatient practice of oncologists. The outcome of treatment is presented in **Figure 6**.



Figure 6. Superficial spreading melanoma T_{3a} N_0 M_0 (stage IIA, according to AJCC classification): (a) before cryodestruction and (b) after cryosurgical treatment.

10. Cryolipolysis

Cryolipolysis or cryo-liposuction is a method of cold destruction of adipocytes and the elimination of gynoid lipodystrophy. Current studies are aimed at determining the mechanism of cryolipolysis but the scientific evidence is still insufficient. At the meeting of the American Society for Laser Medicine and Surgery (ASLMS) in 2012, Dr. Christine C. Dierickx introduced the theory that decreasing temperature in the subcutaneous fat causes energy starvation in adipocytes, which triggers the process of programmed cell death followed by their excretion from the body via the blood and lymph. As the number of fat cells in the hypodermis reduces, its thickness declines from 20 to 25% in 2–3 months after the procedure. This explains the fact that the first result is obtained in a few weeks.

Today, the principle of cryolipolysis is implemented in CoolSculpting ZELTIQ (USA) equipment. This device is approved for use in the Russian Federation. The procedure can be performed on any part of the body except the face, neck, and décolleté. The main condition of the cryolipolysis procedure is the presence of the fat layer 1–2 cm thick. The major advantages of the cryolipolysis method are: liposuction performed without punctures and cuts; the absence of rehabilitation period; and painless procedure and minimum side effects. The indication for the procedure is the local destruction of the excessive fat deposits under obesity of various etiologies.

10.1. Cryo-exposure procedure

Before conducting cryolipolysis, the size and thickness of the fat fold is evaluated and an appropriate nozzle is selected depending on its thickness. Then, a gel is applied to the desired exposure area. A handpiece is placed on the exposure area and the skin fold together with subcutaneous fat is sucked into it. A vacuum is created. Cryo-exposure is performed for 60 minutes. The power and speed of exposure are controlled by the device software. To maintain the normal blood circulation in tissues, vibratory massage starts simultaneously with the local cooling.

After removing the applicator, the skin hyperemia in the “capture” area can be active and passive; its manifestations are terminated after 20–30 minutes. At that time, the patient can perceive chills and hypoesthesia of the skin surface subjected to cryolipolysis. These phenomena are terminated spontaneously within 20–30 minutes and they do not require medical correction.

Possible complications include persistent manifestations of venous hyperemia and prolonged hypoesthesia of the local skin area.

The result can be seen 4 weeks after the procedure. The amount of fat tissue in problem areas is reduced by 2–4 cm in volume. The thickness of the fat fold is reduced by 3–5 cm. As a rule, three to four treatment sessions of 1 hour each are needed for the maximum effect 3 months after conducting cryolipolysis.

The most significant disadvantages of this method are: high cost of the procedure; delayed result; low efficiency in slack skin; one-step reduction of adipose tissue can be performed only for one area of the body; destruction of the excess fat deposits is possible on the localized areas only; a wide range of contraindications for cryolipolysis procedure: obesity grade II and III; electric cardiac pacemaker in the body; pregnancy and lactation; vascular diseases; blood diseases; renal and hepatic failure; diabetes; and Raynaud's syndrome.

Thus, the advantages of the local cryolipolysis method compare poorly with its disadvantages against the wide range of contraindications and a number of significant drawbacks, which sharply limit the implementation of this method into wide practice.

11. Treatment for hypertrophic scars

Reparative processes (postsurgery, or after thermal, chemical, or mechanical injury) that take place in the skin and develop against disturbed local processes of proliferation and differentiation, with an excessive growth of scar tissue, result in the formation of a keloid or a hypertrophic scar.

Hypertrophic scars expand up to 3 mm above the skin surface. The scar growth is initiated immediately after healing, which distinguishes it from keloids. The color of hypertrophic scars may be of pinkish or reddish shade. A mature hypertrophic scar ceases its growth and turns pale within the same time interval as a normotrophic scar. The primary clinical sign of keloid scars (or keloids) is their capacity for continuous growth. Regardless of the scar age, keloids can be active (proliferating) and inactive (stabilized), with alternating periods of rest and of increased growth. An active scar elevating above the level of the skin considerably, becomes palpably dense and red with a cyanotic shade. Keloids and hypertrophic scars can appear not only from the skin injury but also from the resolution of certain dermatoses. The incidence of keloid and hypertrophic scarring, complexity, and duration of their treatment, as well as predisposition to relapse determine the urgency of the problem considered in this monograph.

Emergence of the postoperative keloids and hypertrophic scars at the sites of resolved acne is not uncommon. A number of authors mention that this cosmetic defect leads to psychoemotional disadaptation of patients manifested by a decreased self-esteem, various psychological, and in some cases, psychosomatic disorders. Therefore, elimination of cosmetic defects plays an important role in the social and interpersonal adaptation of such patients.

Multiple attempts to find a method for effective scar correction were undertaken throughout the twentieth century. The most significant and numerous were the methods concerned with the local influence upon the excessive keloid tissue. Thus, the core of the problem lies in the frequent scar recurrence after their "successful" elimination at the sites of primary occurrence, rather than the lack of methods for their destruction or removal. Despite the extensive armamentarium of surgical, radiotherapy, and medication treatment methods, the proportion of recurrence remains quite high, since none of the suggested methods suppresses keloid growth zones, as evidenced by a number of studies.

Keloid and hypertrophic scars bear clinical similarities but differ by their morphology and pathogenetic mechanisms of development. The major differences relate to the structure of the microvasculature, type of collagen that forms connective tissue, cellular composition, and the structure of intercellular substance [12].

The presence of immature connective tissue is typical for keloid scars; it is characterized by an increased content of hyaluronic acid and collagen type III, both possessing high hydrophilic properties. Poorly differentiated (immature) cells, juvenile and atypical giant fibroblasts are predominant. “Young” and “old” keloid scars also have morphological differences. The structure of a “young” keloid is characterized by the presence of four zones: epidermis, subepidermal zone, growth zone, and deep zone. The growth zone represents keloid tissue. This is a young connective tissue, where numerous young fibroblasts are identified, 92 ± 35 cells in the visual field. The presence of giant forms of fibroblasts is typical. The deficit of blood capillaries was detected (0–1 capillary in 1–3 visual fields) in the “young” keloid tissue. “Old” keloids are characterized by the appearing signs of maturation. The growth zone is partially reduced, fibrosis increases, the number of fibroblasts declines and vascularization expands (0–3 capillaries in a single visual field), and the zones of dystrophic and necrotic modifications emerge. At the same time, the signs of activity (foci of young connective tissue) are present.

Hypertrophic scars have another morphological structure. The zones of epidermis and scar tissue are identified there. The number of fibroblasts is less than that in keloid tissue (59 ± 2 in the visual field), with the predominance of mature forms. Vascularization in the hypertrophic scar tissue is increased (3–5 capillaries in the visual field), which determines the biosynthetic activity of mature fibroblasts and the excessive growth of collagen type I.

In this aspect, the cryogenic method of scar treatment is the most advantageous, because the mechanism of cryogenic destruction is correlated with the specifics of subsequent reparative processes in tissues. The treatment for hypertrophic scars is targeted at microcirculatory vessels of the skin, and for keloids—at both the capillaries and the hydrophilic immature connective tissue, rich in fibroblasts that are extremely sensitive to ultra-low temperatures.

Thus, the mechanism of local cryo-exposure is justified pathogenetically and includes two stages. At the first stage, the cells are destroyed directly through the action of ultra-low temperatures, while at the second, destruction of tissues occurs, due to hemodynamic disturbance.

The morphological study of cryobiopsy samples taken from scar tissue 30 minutes after the three-cycle cryo-exposure demonstrated the presence of degenerative changes in all zones, including the growth zone. Fibroblasts had necrotic modifications and the blood capillaries were under destruction. The microhemodynamics blockade increases destructive changes in the tissue. The study of scar tissue samples collected after cryogenic exposure indicates that this method allows to completely destroy the mass of scar tissue (keloid or hypertrophic scar). This is evidenced by the destruction of microcirculatory vessels and the total necrosis of fibroblasts identified in all areas of the keloid scar and in the hypertrophic scar tissue. In 3–4 months, a regenerate is formed at the site of the former scar, which has the appearance of a normal skin and the structure similar to that of organotypic regeneration.

11.1. Cryo-exposure procedure

Prior to performing cryodestruction, we determined the linear dimensions and the projected area of the scar, as follows. First, the colorant was applied to the skin surrounding the scar deformation using the coloring rod. Then the scaled millimeter paper was imposed on the stained surface in such a way that one of the mapping directions coincided with the greatest length of the scar. Linear dimensions were determined on the obtained imprint, according to the millimeter grid, as the distance between the two most distant points located on the long axis of the unstained spot and the length of the perpendicular to this axis corresponding to the scar section in the region of its greatest width. In case the scar is not stretched relative to the skin surface, its diameter is taken as its linear dimension and the scar area is calculated by the formula:

$$S = a + b/2 \quad (1)$$

where, S is the area of pathologically modified skin site, a is the number of totally unstained millimeter squares within the unstained spot, b is the number of partially unstained millimeter squares within the unstained spot.

At first glance, this step may seem tedious and useless but actually it has great practical importance for the choice of cryodestruction method. Treatment for keloid and hypertrophic scars should involve a sufficiently deep cryogenic destruction of pathological tissue and be always accompanied by the subsequent formation of multiple vesicles and/or bullae at the site of exposure.

When the scar area is up to 20 mm², cryo-exposure without adhesion is applied by cryoinstruments chilled passively or actively, by smoothing the scar surface and stopping the applicator for 2–5 seconds at each site.

When the scar area is 20–35 mm², a stepwise freezing of the entire scar surface is applied by touching it with a drop of atmospheric oxygen passively liquefying on the lateral side of the non-thermally insulated cannula and flowing down to the “Ledok” cryoapplicator.

When the scar area is 35–55 mm², a prolonged exposure is applied, a slow rolling of the cotton wool tampon with braided mesh-like surface, chilled in liquid nitrogen, along the scar until a stable, visible for 4–5 seconds freezing of the scar tissue occurs.

When the scar area is over 55 mm², a prolonged cryo-irrigation with liquid nitrogen is applied until a stable, visible for 5–10 seconds, icing of the entire scar surface occurs, with two to three iterations of freeze-thaw cycle at each site during one procedure.

When scar deformities are extensive, a combination of methods is recommended. In order to smooth the surface of atrophic scar, cryotherapy with liquid nitrogen is performed as topical applications.

Along with the destruction of hypertrophic and keloid tissues, cryo-exposure aids in restoration of skin sensitivity and elimination of functional disorders caused by pathological scars.

In this case, the effect is determined by a direct damage to pathological cells and modified microcirculation under the influence of extremely low temperatures.

In conclusion, it needs to be emphasized that four main goals should be pursued in developing the plan and schedule for keloid and hypertrophic scar treatment: functional rehabilitation of the affected anatomical segment, reduced manifestation of local symptoms, improved esthetic appearance and prevention of relapse. The absence of a relapse within 2 years represents a guarantee of successful treatment.

12. Treatment for acne

Acne is a polymorphic disease and one of the most common skin dermatoses with characteristic clinical manifestations in the form of non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, nodes) elements. The lesions are mainly localized in sebaceous zones: face, neck, shoulders, chest, and upper back.

Consensus conference organized in 1990 by the American Academy of Dermatology (AAD) discussed the challenges of developing a standardized and reproducible system for acne classification, with special reference to high polymorphism of lesions, diverse combinations of acne elements, variability in the course of the disease, severity and density of inflammatory lesions at different localizations in the same patient. In accordance with the AAD recommendations adopted in 1991, grading acne severity is evaluated by the number and nature of lesions, distinguishing between the mild, moderate, severe and very severe grades. However, the lack of precise quantitative gradation complicates their practical application. According to the classification adopted at the 20th World Congress of Dermatology [13], acne disease is classified into the mild, moderate and severe grades, where the comedonal and papulopustular (up to 10 elements) forms are referred to as “mild,” papulopustular (more than 10 papulopustules and up to 5 nodes) and nodular (more than 5 nodes)—to “moderate,” and the abscessed and conglobate forms—to “severe” grade.

Despite the large number of dedicated studies, acne still persists as the most common dermatoses in young people. The most widespread clinical variety is *acne vulgaris*, which peaks at the age of 14–17 years old. This draws special attention to the treatment of this dermatosis in adolescents. By quoting Sulzberger [14], “There is probably no other disease that causes more mental stress, misunderstanding between children and parents, the greater overall lack of self-confidence, as well as a lot of mental suffering, as acne,” we can unhesitatingly agree that this statement reflects expressively the problems of relationship between the acne and the psyche.

With view of such facts that lesions are localized on the face skin and that the face represents the major link in interpersonal communication, there is no doubt that acne affects the emotional status of any patient. Hautmann and Panconesi [15] refer the acne to the group of dermatoses, which trigger somatopsychic resonance due to the actual or perceived esthetic discomfort. Both Russian and foreign researchers indicate that skin problems, if accompanied

by psychological fixation on the disease, come as a psychotraumatic factor. Thus, acne has a negative effect on self-esteem and self-perception of patients, interpersonal interactions, and social functions.

These observations demonstrate the formation of such patterns as avoidance behavior, social phobias, anxiety, depression, sensitive reactions, hypochondriacal disorders, suicidal thoughts and attempts, due to acne. The authors agree unanimously that all mental disorders developing against acne cause maladaptation in the social, professional, family life and are able of disrupting compliance with the treatment for skin pathology.

The study performed by Volkova and Glazkova [16] involved collection, interpretation, and integration of clinical data derived from the patients' communications and observations of specialists. Their findings indicate that the overall prevalence of anxiety-depressive mental disorders among outpatients with diagnosed acne amounts to 35.2%, of which anxiety makes 24.2%, depression—26.2%, and mixed anxiety-depressive disorder—43.74%, respectively. Anxiety-depressive disorders reduce greatly the quality of life in patients suffering from acne. The linkage between the Dermatology Life Quality Index (DLQI), Assessment of the Psychological and Social Effects of Acne (APSEA) and mental disorders reflects the relationship between the skin processes and the development of anxiety and depression. Moreover, the objective status of a patient does not necessarily coincide with his/her subjective perception of this disease. Welp and Gieler [17] confirmed this statement in their experimental study by observing patients with a pronounced discrepancy between the objective picture of the disease diagnosed by the physician and the subjective severity of mental suffering.

Moreover, as noted by Bosse and Hunecke [18], the subjective severity of suffering is affected by such factors as localization and visibility, chronic course and skin changes, gender and age, complaints against personal looks, and self-esteem. The subjective perception of ugliness can reduce self-esteem until the paranoid reevaluation the disease's significance. Due to the reevaluation of the somatic phenomenon, the person becomes morose, minimizes communication with surrounding people and tries to avoid external contacts, up to the social isolation. According to Bosse [19], a patient with skin disease is granted only a limited approved social right to make claims; the author calls it "the hypothesis of non-fastidiousness." The role of negative evaluation of one's subjective attractiveness is described in a large number of works, which can be summarized vividly by Bosse's [20] quotation: "Pimples on the face – scars on the soul." Cases of dysmorphophobia are common even with the minimal acne lesions.

Resolution of dermatosis is often accompanied by the development of persistent post-ruptive keloid and/or hypertrophic, atrophic scars, which leads to an uneven skin texture. At the same time, postinflammatory pigmentation disorders make common cases with acne. Emergence of the secondary persistent dyschromia is observed at the sites where dermatosis elements were resolved. Melanin hyperchromia, or local hypopigmentation, in combination with post-ruptive scars, makes a persistent cosmetic defect. Acne disturbs the esthetic effect of the skin and thus has a pronounced effect on the psycho-emotional sphere of the patient and his/her social adaptation. This determines the urgency of developing new adequate treatment modalities for acne to address effectively the healthcare and social problems. Undoubtedly,

all the above mentioned factors underline the need for a novel method of treating acne with a good cosmetic effect, to ensure the esthetic comfort and recover the psychoemotional health. Moreover, treatment should be a short-term and highly effective, in order to avoid psychosocial consequences.

Several important factors are identified in the pathogenesis of acne: hyperplasia and hyperfunction of sebaceous glands, follicular hyperkeratosis, microbial colonization, and inflammation of the sebaceous gland. Inflammation can be both superficial and deep, which brings about a variety of clinical manifestations. A vast number of national and international works is devoted to studying skin micro-landscape in patients with acne. In 1983, V.M. Kovalev studied the microflora of acne elements; 668 strains were isolated and identified, where staphylococci communities and *St. aureus* strains prevailed. This was apparently associated with the presence of excoriations in the area of localized pathological elements, which preconditions higher *St. aureus* incidence under this pathology. Microbial associations were found to be inoculated more often than monocultures. To date, it is commonly believed that acne is closely associated with the excessive colonization of the skin and its appendages by *Propionibacterium acnes* (*R. Acnes*), the dominating follicular resident organism. There exist other opinions but these are in minority.

Given the key role of pathogenic microorganisms in the pathogenesis of acne, the applied treatment modalities become obvious.

Antibiotics have been used for over 40 years until now and they represent a fundamental part of modern acne therapy, as confirmed by the recommendations of the International Union of Acne Treatments (Paris, 2002). The limiting factor to the topical antibacterial therapy is its time length. A lasting positive effect can be achieved only when applied permanently for 4–6 months, because such medications should exercise their curative effect through several periods of the epithelial renewal. Unfortunately, these terms of use involve a high risk of developing resistance. According to Kar [21], the first clinically significant changes in *P. acnes* sensitivity were found in the USA in the late 1970s. Later, in the late 1980s- early 1990s, the comprehensive studies revealed clinically significant resistance to antibiotics and identified strains with multiple antibiotic resistance, as reported by Del Rosso [22]. Moreover, Rivera [23] emphasized that resistance was developed not only by the skin surface bacteria but also microbial populations in the nasal cavity, which is a permanent reservoir of microflora and can reduce the effectiveness of antibiotic therapy. Kirichenko [24] pointed out the fact that microorganisms are characterized by natural and acquired resistance to antibiotics; they survive successfully and retain their virulence, especially in microbial associations. Eady [25] emphasized that patients with developed resistance to local forms of antibiotics were also unresponsive to systemic antibiotic therapy. Moreover, it should be kept in mind that prolonged use of topical broad-spectrum antibiotics can lead to the appearing gram-negative rods on the facial skin that are uncharacteristic of its natural microflora and can eventually result in the development of gram-negative folliculitis, untreatable by traditional methods.

Despite the available abundance of antibacterial drugs, all those have diverse side effects. We will not list in detail the side effects that occur during systemic antibiotic therapy. The most significant complications, such as dysbiosis of various localization, hepatotoxicity, hematologic

reactions, or toxic epidermal necrolysis are known to every physician since student's years. When appointing a certain drug to the patient, a full list of complications and contraindications can be viewed in the national medication registry.

Here, we will only mention that many antibacterial preparations included in the standard treatment plans cause photosensitization and, therefore, an increased risk of dermatoses based on photodynamic reactions. In addition, there is a high risk of medical melanoderma, against the prolonged intake of drugs with pigment-forming properties, which presents an additional cosmetic problem. Moreover, antibiotic treatment can be considered as a major risk factor for scarring, especially in the presence of papules or pustules, since antibiotics trigger the intensified scarring processes in the lesions.

Burkhart and Gottwald [26] indicated the need to develop new technologies in acne treatment aimed at minimizing the use of antibiotics and thus to prevent the development of microflora resistance. We fully share the opinion stated by Zainullina [27] concerning the modern demand for a totally new approach to the effective treatment of various forms of acne.

In 2009, by the decision of the Global Alliance for the Treatment of Acne (GA), retinoids were introduced into the list of drugs of the first choice, in addition to topical antibiotics. The adverse effects of retinoid therapy include xerophthalmia, conjunctivitis, cheilitis, irritative dermatitis, skin xerosis, erythema, nasal hemorrhage, pyogenic granuloma, impetigo, alopecia, Achilles tenosynovitis, hyperostosis, myalgia and arthralgia, hepatotoxicity, neutropenia, benign increased intracranial pressure. However, the most significant complication is teratogenicity. According to Racine [28], 50% of pregnant women under isotretinoin treatment developed grave intrauterine fetal anomalies in the first trimester of pregnancy including pathologies of the cardiovascular system, central nervous system, skeleton and sensory organs.

A trend towards increasing resistance of etiologically significant microorganisms to basic antibiotics used in the standard treatment regimens determines the urgent imperative to find the effective acne treatment. Treatment of various clinical forms of acne is still a challenge, despite the already available algorithms and protocols for patient management. Thus, for example, the effectiveness of antibiotic therapy depends not only on sensitivity, but also on the ability of medications to be delivered to the target organ. Poor skin permeation presents a limiting factor for some antibiotics that have proven high sensitivity of pathogenic microflora. In addition, it is established that *P. acnes* secretes glycocalyx biofilms impermeable to antibiotics. For this reason, topical medications are applied mostly as components of fixed dose combination. Recommendations of the European Dermatology Forum (EDF) for the treatment of acne (2011) emphasized the fundamental importance of combined therapeutic approach to all pathogenetic components in the topical acne treatment, taking into account full diversity of pathogenetic factors.

Resistance of various groups of microorganisms to antimicrobial drugs stated in the treatment algorithms has been studied extensively since 1979 by Russian and foreign authors. Their findings demonstrated the general long-term trend toward increasing resistance of the main microbial agents of pathogenetic significance to the basic antibiotics. Development of resistant strains

and, consequently, reduced effectiveness of antibacterial treatment determine the need for monitoring the microflora of skin biota, together by identifying the sensitivity of cause-significant groups of microorganisms to antibacterial drugs. There is no possibility to perform antibiotics sensitivity tests in routine clinical practice. In this regard, new approaches to the treatment of acne are needed, which would prevent the emerging resistance in cause-significant microorganisms.

The complex nature of pathogenesis dictates the need to affect all pathogenic factors of acne, particularly for local therapy, as confirmed by the EDF recommendations (published in 2016), which reaffirmed the importance of combined therapeutic approach to all pathogenetic components in the topical acne treatment.

However, cryotherapy fully meets all these requirements. We have considered the opinion of Konchugova [29] and developed a non-drug technology for the treatment of acne. The therapeutic effect is based on the normalized microflora of the facial skin and its appendages, improved microcirculation in the foci of dermatosis, eliminated follicular hyperkeratosis, and improved sebum evacuation. Local cryo-exposure causes the destruction of differentiated keratinocytes, intensifies desquamation of epidermal corneocytes and facilitates exfoliation of the epidermis.

The species composition of microbial community and the antibiotic sensitivity of its dominant component can be analyzed endlessly. We have already mentioned the vast amount of relevant studies, which bring only one conclusion – the increasing resistance of microbial associations to the antibiotics. For this reason, we did not investigate the facial microbial landscape with the subsequent determination of antibiotic sensitivity. Sharing the opinion of E. Rivera, we studied the antimicrobial effectiveness of cryotherapy on microbial populations in the nasal and oral cavities under the ENT pathology. Our findings were published in a number of other papers and here we would only notice that there are no microorganisms or microbial associations that are insensitive to ultra-low temperatures.

Skin smoothness was evaluated by the computer analysis of facial skin replicas in patients with severe late acne after cryogenic treatment and in similar patients after traditional treatment. A silicone-based replica reflects all irregularities of the skin microrelief. According to our results, it can be stated unequivocally that cryogenic treatment for acne smoothes the skin micro-relief considerably, thus improving greatly the esthetic posttreatment effect on the facial skin. Due to the labor-intensive process of manufacturing skin replicas, the analysis of images obtained directly with high-resolution digital cameras has become very popular in today's practice.

Evaluation of the immune status in patients with moderate to severe acne prior to treatment demonstrated a decrease in the absolute content of CD3, CD4, CD8, and an increase in CD72. A decrease in the relative and absolute content of T suppressors with the CD4 + and CD8 + markers, B-lymphocytes with the CD72 + marker was characteristic of the patients with papulopustular form. In some cases, a decrease in the absolute content of the total T-lymphocytes with a CD3 + marker and T-helpers with the CD4 + marker was found against the normal values of the total leukocyte and lymphocyte counts.

The immunomodulating effect of cryo-exposure on parameters of the cellular and humoral components of immune system was translated into an increase of conventionally low baseline values for the absolute content of lymphocyte subpopulations with CD4+, CD8+, CD72+ markers

and IgA serum content. In patients with low baseline levels, there was a trend towards an increase in CD4+, CD8+, CD16+, and a substantial increase in CD72+, IgA and IgG in the blood. As regards the humoral component of immune system, IgA and IgG concentrations significantly decreased and IgM concentration increased; these parameters were in direct correlation with CD 72. IL-1 concentration in the blood of patients with acne increases with the increasing disease severity and is increased twice under “severe” grade. These disturbances indicate the inhibition of innate and adaptive immunity and the depletion of reserve capacity of the body.

12.1. Cryo-exposure procedure

Our practice of cryogenic treatment for acne relies upon the AAD classification (modified Russian version), which enables the most adequate selection of the tentative cryo-exposure method:

- Grade I is characterized by the presence of comedones (open and closed) and up to 10 papules;
- Grade II is characterized by the presence of comedones, papules, and up to 5 pustules;
- Grade III is characterized by the presence of comedones, papulo-pustular rash, and up to 5 nodes;
- Grade IV is characterized by a pronounced inflammatory reaction in the deep dermal layers, along with soreness and ulceration, formation of fistulae and nodulocystic elements.

Inverse acne (*acne inversa*), conglobata-cystic acne (*acne conglobate*), and resistant acne are subjected to cryogenic treatment in line with our method developed for the Grade IV acne severity, according to the above classification. To implement these techniques, we use a set of instruments for medical cryology developed by Dr. V.I. Kochenov. Prior to the start of cryo-exposure, the facial skin is wiped with a cotton tampon moistened with 3% salicylic acid alcohol solution and a drop of 10% glycerol solution is applied to each acne element. Given the high polymorphism of lesions, diverse combinations of acne elements, and to improve the effectiveness of treatment, we apply a combination of cryogenic methods.

Acne severity Grades I and II: cryodestruction of each acne element with cryostick chilled in liquid nitrogen. Cryo-exposure is continued until the complete icing of the pathological element. Each cryo-manipulation consists of three freeze-thaw cycles. Then, a prolonged cryo-exposure is performed by rolling a cotton wool tampon with a woven mesh surface, cooled in liquid nitrogen, over the entire face skin (and/or other site with signs of dermatosis), until a stable, persistent for 4–5 seconds, visible freezing track occurs.

Grade III: cryo-irrigation with liquid nitrogen of each acne-element using a nozzle for interstitial linear freezing, until a stable, visible for 5–10 seconds icing of the entire surface of the pathological element occurs, with two to three iterations of the freeze-thaw cycle at each site during one procedure.

This is followed by the facial cryomassage (and/or other site with signs of dermatosis), according to the technique described above.



Figure 7. Facial skin in a female patient with acne disease, severe grade (a) before and (b) after completed treatment course.

Grade IV: consecutive freezing of pathological acne elements by applying a drop of atmospheric oxygen liquefied passively on a cannula (4 mm), using “Ledok” cryoapparatus with an oval pointed applicator. Each acne element is subjected to cryo-exposure three times. Then, cryomassage of facial skin (and/or other site with signs of dermatosis) is performed with a roller cooled in liquid nitrogen, until a visible white freezing trace is formed.

Our treatment method for *provoked acne* (*acne artificialis*, acne mechanica, acne venenata, contact acne, acne toxica, acne de la brilliantine, acné excoriée des jeunes filles) and Gram-negative folliculitis involves topical application using an applicator with the meshed-cellular elastic surface, 7–10 cm long, fixed to the handle. The applicator is moistened with liquid nitrogen, placed parallel to the treated surface and is slid in continuous rotational movements, under light pressure from the operating hand, over the affected surface until the minute skin whitening is formed.

Cryo-sessions are conducted once or twice per week. Depending on the acne severity, the course includes 10–15 procedures.

Cryogenic treatment for acne affects successfully three key components of pathogenetic significance through normalizing the sebum evacuation and destroying microbial associations and thus it arrests inflammation. At the same time, cryo-exposure triggers a pronounced immunomodulatory effect. The clinical effectiveness of cryotherapy is translated into the shorter time of treatment, the longer remission period, as well as the prevention of postoperative scarring and persistent dyschromia.

Its high efficiency is based on the marked compensation of the initial microcirculatory disturbances and the immunocorrecting effect on both the cellular and humoral immunity, which is manifested in the normalized ratio of immunoregulatory subpopulations of T-lymphocytes, increasing their functional activity, and recovery of serum immunoglobulins A and G up to

their normal level. Moreover, ultra-low temperatures destroy melanocytes, thereby preventing traumatic pigmentation and local melanodermy. Additionally, the obtained morphological data prove that cryodestruction provides an effective treatment method for postoperative keloids and hypertrophic scars, ensuring their complete destruction and the subsequent skin regeneration, similar to that organotypic regeneration. The outcome of treatment is presented in **Figure 7**.

13. Conclusion

Dermatoses, in particular, acne and psoriasis, can provoke sensitive reactions and hypochondriac disorders. Obviously, formation of secondary (in relation to the somatic pathology) mental disorders depends on a number of social and demographic factors, specifics of the primary disease, and premorbid properties of the person, but eventually they only emphasize the significance of this problem. In addition, the internal picture of the disease, as the major complex of secondary psychological symptoms, can complicate the course of the disease in certain cases, hinder the success of therapeutic measures, and slow down the rehabilitation. Treatment for dermatoses is in need and the effective treatment is in double need. Treatment of all dermatological pathologies can not be described just in one chapter and for this reason the priority was given here to the most common dermatoses. Our current work includes development of a guideline for physicians "Cryogenic treatment methods in dermatology" (the tentative title).

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