

TRANSDERMAL THERAPEUTIC SYSTEMS–AN INNOVATIVE METHOD TO PREVENT THE FORMATION OF KELOIDS

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ABSTRACT

Modern medicine has achieved significant results in the development of techniques to avoid surgeries. However, surgical methods are still one of the main tools for treating pathologies in the human body. Plastic surgery and cosmetology are gaining popularity every year, and sports injuries require the use of combined treatment methods, but any such intervention leads to the risk of keloids. The younger the person, the higher the likelihood of developing a keloid, due to the high degree of elasticity of the skin at an earlier age, which is prone to scarring than in older people. Women are at higher risk of developing keloids than men because their skin is more elastic. Thus, children and young women are most at risk of keloid formation, both as a result of physiological processes of skin scarring and preference for plastic surgery, cosmetic procedures and other methods of correction. In world pharmaceutical practice, there are not enough existing ways to prevent the development of keloid. It is necessary to conduct research on the selection of a fundamentally new structural basis for a transdermal therapeutic system containing the most effective and safe compounds of the regenerating and antioxidant mechanisms of action (vitamins and other biologically active compounds) from the point of view of preventing the formation of keloids, which will help in solving the problem of not only preventing the formation of keloids in the dermis, but also its subsequent growth and exit to the surface layers of the skin.

Keywords: Scar tissue (scar), Keloid scars (keloids), Pathological scarring, Scar treatment methods, Transdermal therapeutic systems

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INTRODUCTION

The formation of keloids (keloids) after surgery is a common clinical and cosmetic problem. To date, it is impossible to determine in advance the likelihood of the appearance of such pathological formations in the postoperative period in a particular patient. The reason for this lies in the limited amount of theoretical and practical material accumulated by modern medicine to understand the causes of this kind of complication, as well as knowledge of the cellular and molecular mechanisms of their further development. However, it has not only been noticed but also proven that a high risk of keloid formation is characteristic of those areas of the human skin that, on the one hand, have a high skin tension, and on the other hand, have a tendency to delayed healing: the anterior chest wall, mammary glands, earlobes, corners of the lower jaw, shoulder blades, elbows, knees. In addition to psychological problems, this can lead to disruption of such physiological processes as, for example, flexion and extension of the feet, hands, fingers and toes [1].

When writing this review, materials of doctors specializing in the treatment and prevention of skin scars of various etiologies were used [1, 2, 6].

Scar tissue classification

A scar is a dense connective tissue formation that has arisen as a result of tissue regeneration after damage or inflammation [2].

According to the classification given in the book of Ozerskaya O. S. «Scars of the skin and their dermatocosmetological correction», there are 4 types of scar tissue: [3]

1. Normotrophic scar tissue (fig. 1) has a pale color, does not change the general relief of the skin surface, has normal or reduced sensitivity and elasticity. The formation of normotrophic scar tissue is a physiological process.
2. Atrophic scar tissue (fig. 2)–has a pale color and reduced sensitivity, located below the level of the surrounding skin. Atrophic scar tissue is formed in places of tissue tension, with the introduction of corticosteroids into immature hypertrophic scar tissue, during pregnancy, endocrinological diseases; at the same time, it does not cause functional disorders but presents a serious aesthetic problem.



Fig. 1: Normotrophic scar

3. Hypertrophic scar tissue (fig. 2)–mature connective tissue protruding above the level of the surrounding skin, covered with a layer of epidermis and located strictly in the area of damage. In the first months after the appearance, hypertrophic scar tissue has a red or cyanotic color, at this time, its development is accompanied by itching, paresthesia and hyperkeratosis (fast-growth phase). After about six months, the phenomena of inflammation and progression of hypertrophic scar tissue stop, it turns pale, its height decreases above the level of the surrounding tissues, gradually decreases in size over several years, sometimes leading to small flat scars without further symptoms, the likelihood of recurrence is low [4]. However, this type of scar tissue is the most common and represents not only an aesthetic but already a functional problem since contractures and syndactyly are formed, which are often ulcerated and malignant. The main factors contributing to the formation of a hypertrophic scar are: hyperergic reaction of connective tissue to injury; relatively unfavorable conditions for wound healing; lack of prevention of education in the post-traumatic or postoperative period.

4. Keloid scar tissue (fig. 2) is a dense, rather sensitive, convex tumor with a shiny surface, thinned epithelium and limited erosive areas, which usually persist for a long period of time and do not disappear spontaneously [4, 5]. Keloid scar tissue is characterized by

spontaneous formation even with superficial damage, unrestrained growth, pronounced symptoms of inflammation and spread to intact skin areas, has an elastic consistency, an uneven, slightly wrinkled surface; thickens and grows at the edges, but never flakes or flakes. The area of the keloid scar is many times larger than the area of the previous wound. The main sign of keloids is persistent progression, spreading to intact surrounding tissues. The likelihood of recurrence of a keloid scar is high [6].

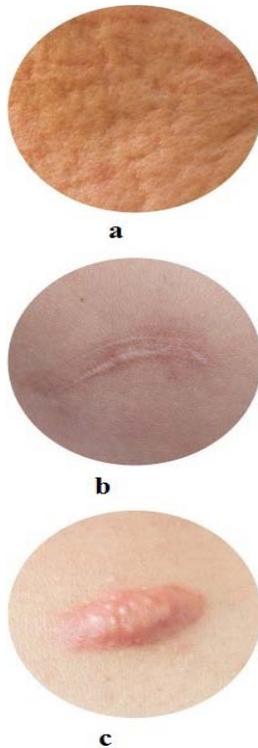


Fig. 2: Pathological types of scars (a-atrophic scar, b-hypertrophic scar, c-keloid scar)

Stages of scar formation and wound healing

Currently, there are three stages of scar formation: [7]

- 1) Fibroblastic stage (up to 30 d)–characterized by epithelialization of the wound defect, an abundance of blood vessels and proliferation of young fibroblasts, the formation of a large amount of amorphous substance and the production of reticular fibers;
- 2) Fibrous stage (30-40 d)–characterized by the accumulation of mature fibroblasts synthesizing collagen fibers;
- 3) Hyaline stage–characterized by hyalinosis of collagen fibers of scar tissue, a decrease in the number of fibroblasts and blood vessels.

Wound healing is conventionally divided into three overlapping phases: the inflammation phase, the granulation tissue formation phase, and the matrix formation phase, or the remodeling phase. The second phase of wound healing (granulation), characterized by the formation of granulation tissue, already forms the prerequisites for the development of scars. In the granulation phase, the processes of angiogenesis, re-epithelialization and collagen synthesis take place. Remodeling is the third and final phase of wound healing when the extracellular matrix is reorganized. In this phase, wound contraction also occurs, which is a complex interaction between fibroblasts, fibronectin and collagen [1, 5, 8].

Prevention of pathological scarring

The main areas of scar prevention are:

1. Correct management and treatment of wound surfaces of burns, injuries, cosmetic procedures and surgical interventions:

- a) The location of the incision line perpendicular to the main direction of muscle contractions in various anatomical zones of the face;
- b) Ensuring adequate long-term immobilization in the area of the surgical intervention (when using adhesive coatings with silicone gel–for 2-3 mo and at least 12 h a day);
- c) Adherence to the stages of treatment and time ranges.

2. Prevention of postoperative complications, since complications can cause expansion of the area of skin destruction and additional scarring.

3. Correction of the emotional-volitional sphere, attitudes, interests in patients with cicatricial skin lesions; in addition to scar therapy, it is necessary to carry out psychological work aimed at restoring the psyche of patients since the best treatment result is achieved with the interaction of specialists from related specialties. Comprehensive, timely specialized care allows to ensure the optimal aesthetic and functional effect of treatment and complete rehabilitation [2, 6].

However, at this stage in the development of medicine, there are insufficiently effective methods for preventing the appearance of pathological scars. Modern strategies for the correction of this disease are based on a rational combination of surgical and conservative interventions [9-12]. Physical and physiotherapeutic methods (the use of occlusive dressings, compression and laser therapy, cryosurgery, electrophoresis, etc.), radiation therapy to prevent relapse, as well as cosmetic procedures aimed at external correction of the defect and not bearing any therapeutic purpose (peeling, mesotherapy, dermabrasion) [1, 4, 13-15].

Scar treatment methods

Surgical treatments (table 1)

Surgical treatment is carried out with formed pathological scars when conservative methods of treatment are ineffective. The choice of a surgical method depends on the type of scar, its size and location, the depth of the scar lesion and its area, as well as the severity of the functional disorders and cosmetic defects caused by it. Surgical methods are effective for keloid (mainly) and hypertrophic scars [3, 6, 16-19].

The nature of scarring largely depends on the anatomical and physiological characteristics of the tissues surrounding the scar and the methods of wound closure. Surgical methods of treatment help to eliminate excessive tension in tissues that predispose to hypertrophic scarring.

1. Closing the wound in favorable conditions by simple excision of the scar followed by stitching the edges of the wound (aimed at the formation of a thinner scar, shown with a relatively small width of the scar and good mobility of the edges of the wound), mobilization of tissues and joining them with one of the methods (depending on the depth of the wound–strips of plaster, removed with continuous intra- or epidermal sutures, non-removable absorbable subdermal sutures with the additional imposition of a subsequently removed suture, multilayer sutures). Plastic surgery with local tissues (plastic with trapezoidal or counter-triangular flaps)–the main principle of such surgical correction was to change the direction of the scar. These methods were used for limited cicatricial cords.

2. Closing the wound in unfavorable conditions by moving local flaps, split skin grafts, normotension using tissue expanders. The method that allows you to obtain material identical to that lost in color, structure, elasticity, hair, is dermatension–implantation under the nearby intact skin of expanders, dosed stretching of the skin and plastic wound formed after excision of the scar. The use of expanders made it possible to obtain an increase in healthy tissues, that is, a plastic material that did not differ in properties from normal skin. Expander dermatension expands the ability to eliminate extensive keloid scars and cicatricial deformities [2, 6, 20, 21].

3. Closure of extensive tissue defects by moving complex tissue complexes from distant areas while maintaining blood supply.

Scheme of surgical correction of keloid scars

- 1) In combination with conservative treatment;

- 2) A needle prick during infiltration should be placed only on those areas of the skin (scar) that are to be removed;
- 3) Dissect the tissues with the sharpest possible scalpel to the subcutaneous layer to the full depth;
- 4) Do not touch the dermal layer of the skin with instruments;
- 5) The edges of the wound are brought together with a continuous removable suture, applied in the subcutaneous fat layer;
- 6) Apply strips of plaster (Steri-strip) to skin wounds;
- 7) When the skin wound is pulled, the defect is closed with a thin skin graft, the edges of which extend beyond the skin wound and are fixed with a plaster to the surrounding skin;
- 8) Tissue immobilization [2].

Considering the fact that surgical treatment of keloid scars (the most difficult variant of the development of pathological scarring) in 50-100% of cases leads to even more severe relapses, the methods of their pharmacological correction play a special role [1, 22-24].

Cryodestruction (table 1)

Cryotherapy has been used as an alternative surgical method for the treatment of hypertrophic and keloid scars. Liquid nitrogen freezes the scar tissue (the microcirculatory bed is affected, which causes cell death through the formation of intracellular crystals), followed by their thawing (the result is tissue necrosis and rejection). Cryotherapy can be painful and traumatic and cause depigmentation. After cryodestruction, the inflammation process lasts from 3 w or more. Some authors considered it expedient for the treatment of hypertrophic scars to try destruction in an isolated form, and for the treatment of keloid scars—the cryogenic microwave method [6, 17, 25, 26].

Cryosurgery can be used both independently and in combination with microwave irradiation. The advantage of cryosurgery is the absence of gross scarring. Disadvantages of cryosurgery: long-term healing of an open wound surface after the intervention, local pain, difficulties in choosing an adequate freezing time and the number of procedures. Side effects are inflammation and soreness of the open wound surface, atrophy and persistent hypopigmentation. Another type of cryosurgery is cryodermabrasion, namely gas-liquid exposure (air, oxygen, carbon dioxide)—removal of the surface layer of the skin in the area of the scar by means of a gas-liquid jet to «blood dew». Indications for this procedure: hypertrophic, keloid scar; atrophic skin changes (striae); acne [2].

Radiation therapy and X-ray therapy (table 2)

Various radiation sources are used: beta applicators, iridium-192, strontel, megavolt and electron beams. For a successful correction result, the radiation dose is more important than the timing of its initiation. Side effects: skin atrophy, telangiectasia, pigmentation disorders, ulceration, alopecia, radiation dermatitis, recurrent lesions [2].

The effectiveness of radiation therapy is disputed. The method is used to treat predominantly keloid scars in the form of monotherapy (relapse—in 50-100% of patients), but more often—in combination with surgical excision and is one of the old methods of treatment. Due to its carcinogenic effect, radiotherapy is used only in the most extreme cases. Does not apply to the head, face, chest area. Currently, the use of radiation therapy is severely limited. X-ray therapy (Bucca rays) is based on the action of ionizing radiation on the connective tissue, causing swelling and destruction of collagen fibers, fibroblasts. X-ray therapy has a number of side effects, so its use is also sharply limited [3, 6, 17, 21, 27].

Table 1: Surgical and cryosurgical treatments for scars

	Surgical methods	Cryosurgical methods	References
Application area	keloid and hypertrophic scars	keloid and hypertrophic scars, atrophic skin changes (striae), acne	[2, 6]
Dignity	help to eliminate excessive tissue tension that predispose to hypertrophic scarring	no rough scarring, can be used both independently and in combination with microwave irradiation	[2, 6]
Disadvantages	surgical treatment of keloid scars in 50-100% of cases leads to even more severe relapses	long-term healing of an open wound surface after the intervention, local soreness, difficulties in choosing an adequate freezing time and the number of procedures, inflammation and soreness of the open wound surface, atrophy and persistent hypopigmentation	[1, 2, 6]

Laser therapy (table 2)

Laser therapy is used to destroy abnormal tissue in order to reduce the risk of abnormal scarring. Currently, laser therapy is used more widely and mainly in combination with other methods. Most often, a combination of a modern yttrium aluminum garnet laser (wavelength 1064 nm) and steroid injections are used to achieve a stronger scar flattening. Some authors note a stable clinical result

when using an infrared laser (wavelength 540 nm) against the background of diprospan injections, etc.

Laser therapy in comparison with the physical methods described above has a number of advantages: the accuracy of local exposure; the ability to control the depth of impact; minimal damage to healthy tissue; sparing effect on the skin (tissue burn and vascular coagulation are minimal) [3, 6, 25, 28, 29].

Table 2: Application of radiation therapy, X-ray therapy and laser therapy in the treatment of scars

	Radiation therapy and X-ray therapy	Laser therapy	References
Application area	Keloid scars (as monotherapy, and also in combination with surgical excision, but not applied to the head, face, sternum)	Destruction of pathological tissues in order to reduce the risk of pathological scarring (in combination with other methods)	[3, 6]
Advantage	No (outdated method of treatment, currently use is sharply limited)	The ability to control the depth of exposure, minimal damage to healthy tissues, gentle effect on the skin	[3, 6]
Disadvantages	Skin atrophy, telangiectasia, pigmentation disorders, ulceration, alopecia, radiation dermatitis, recurrent lesions	Tissue burns and vascular coagulation are observed, however, the degree of their damage is minimal	[2, 3, 6]

Cosmetic procedures (table 3)

Cosmetic procedures are aimed at aesthetic correction; the use of these methods is rational for the correction of small scars. The most popular procedures are peeling, mesotherapy, dermabrasion, etc. [6, 18, 25, 30, 31]

Chemical peeling is suitable for atrophic and hyperpigmented scars post-acne. Contraindications: congenital ectodermal dysplasia, radiation dermatitis, scleroderma, infectious skin diseases, multiple birthmarks, extensive and deep cicatricial lesions, a history of post-inflammatory pigmentation or melasma, a predisposition to hypertrophic scarring [2].

The purpose of dermabrasion is to even out the relief and color of this area. The indications for this procedure are: alignment of the relief of superficial extensible protruding scars, up to 1.0 cm in width in terms of 6-8 w to 6 mo after surgical treatment or a scar in the stage of formation. Dermabrasion is not a radical treatment for scars, but it allows you to bring the condition of a hypertrophic scar closer to a neurotrophic one: using sandpaper, a scalpel, a diamond bur to «blood dew» level the surface, achieve uniform normal pigmentation, elasticity and softness of tissues. In aesthetic medicine, mechanical and laser dermabrasion are used with various options for closing a postoperative wound. Side effects: hypo- or hyperpigmentation, prolonged erythema (within 1-2 mo), telangiectasia, petechiae, hypertrophic scarring, infection of the wound surface [2, 6].

Botulinum therapy helps to relax the facial muscles and reduce tension in the area of the forming scar. Another type of cosmetic scar

correction methods is contour injection plastic-injection use of implant materials (based on hyaluronic acid) and fatty autografts with preliminary undercutting of scar-altered skin. Indications: a deficit in the volume of integumentary tissues, as well as localization no deeper than subcutaneous fat and no more than 15 mm in diameter and the formation of an interstitial cavity. A contraindication to this procedure is severe atrophy of the scar-altered skin [2].

The most high-tech are the use of biological dressings-xenoskin, cultured human cells, wound dressings, etc. However, all the above-described hardware methods for treating scars are traumatic, expensive, have many contraindications (autoimmune diseases, laminopathies, etc.), require an individual comprehensive approach and appropriate technologies [6].

Table 3: The use of cosmetic procedures in the treatment of scars

	Chemical peeling	Dermabrasion	Contour injection plastic	References
Application area	Aesthetic correction of small scars			[6]
Advantage	Suitable for atrophic and hyperpigmented scars, post-acne	Allows you to bring the state of a hypertrophic scar to a normotrophic one by leveling the relief of superficial extensible protruding scars (after surgical treatment or if the scar is in the stage of formation)	Injection use of implantation materials (based on hyaluronic acid) and fatty autografts with preliminary undercutting of scar-altered skin is used in case of a deficiency in the volume of integumentary tissues	[2, 6]
Disadvantages	A large number of contraindications: congenital ectodermal dysplasia, radiation dermatitis, scleroderma, infectious skin diseases, multiple birthmarks, extensive and deep cicatricial lesions, a history of post-inflammatory pigmentation or melasma, a predisposition to hypertrophic scarring	Serious side effects: hypo- or hyperpigmentation, prolonged erythema (within 1-2 mo), telangiectasia, petechiae, hypertrophic scarring, infection of the wound surface	A contraindication to this procedure is pronounced atrophy of scar-altered skin	[2, 6]

Cellular technologies

Cellular technologies have been actively used in recent years to improve the appearance of scars. The interest in the application of cellular technologies in dermatocosmetology is due to the fact that «cellular compositions» carry a powerful bioenergetic and informational potential, thanks to which it is possible to obtain qualitatively new treatment results. The autokines secreted by the transplanted cells (growth factors, cytokines, nitric oxide, etc.) primarily act on their own fibroblasts—the key cells of the dermis. It is known that after trauma to the skin with a catheter, laser, needle and other instruments, from the bone marrow, adipose tissue and capillary pericytes, the skin is replenished with fresh stem precursors of fibroblasts, which contributes to the «rejuvenation» of the pool of its own cells. They actively begin to synthesize collagen, elastin, enzymes, glycosaminoglycans, growth factors and other biologically active molecules, which leads to an increase in hydration and vascularization of the dermis, an improvement in its strength. Currently, neofibro-lifting is used to reconstruct the microstructure of the dermis with superficial scars, photoaging, etc. Transplantation of autologous dermal fibroblasts using intradermal injections (from 30 to 60 million autofibroblasts once, 1 time per month) depending on the focus of correction. The material for autofibroblasts is the skin behind the ear in patients. The introduction of autofibroblasts, while creating the necessary conditions for their engraftment and functioning, promotes the formation of the extracellular matrix and new collagen. After one month, against the background of standard cosmetic procedures for caring for the lesion, it is necessary to individually maintain the achieved results aimed at preserving water resources, microcirculation and the volume of nutrients. There are only immediate results of treatment [6, 32-39].

Compression (table 4)

Constant compression 20-40 mm hg. art. applied 12-24 h a day for 3-12 mo. On the one hand, it resists the growth of scar tissue, mechanically holding it in a limited space; on the other hand, by

squeezing the vessels of the scar, it blocks its nutrition, which leads to a cessation of its growth and partial regression [6].

Varieties of compression (pressure) dressings: silicone plates or coverings with silicone gel; the use of elastic roll and tubular bandages applying constant pressure on the skin in the range of 30-40 mm hg. art. with difficulties in fixing the coating with silicone gel; fixation with adhesive plaster; transparent face masks; acrylic splints, apparatus, and devices for enhancing compression on the forming scar tissue. Contraindications: acute or aggravated chronic infectious skin diseases, persistent postoperative sutures, open wounds, allergic skin reactions. Complications with prolonged use: exacerbation of concomitant chronic skin diseases, secondary infection, slowing down of regeneration processes in the wound [2].

Compression garments immobilize and reduce tissue tension. It is recognized as a first-line remedy, included in the world standards for scar prevention, is sewn from special materials according to special patterns so that the pressure on each centimeter of the skin is 25 mm hg. art. Wearing compression clothing is indicated when there is a threat of the formation of extensive scars after injuries, burns. Dosed pressure on the scars causes them to turn pale and soften up to complete smoothing [2].

Silicone gel dressings have been widely used in the treatment of hypertrophic scars and keloids since the early 1980s. In 1982 K. Perkins *et al.* for the first time, reported on the use of silicone gel plates in post-burn scars and contractures [6, 40]. Over the past decades, a large number of works have been published showing the positive effect of silicone preparations on the condition of scars [9-12, 24, 41-43]. Silicone plates and patches prevent excessive scarring by applying even pressure to reduce the volume of the extracellular matrix and promote parallel collagen fibers. The expediency of using silicone gels for the treatment and prevention of scars—the preparations «Dermatiks» and «Kelo-cat», has been proved. After drying, they form the thinnest coating on the skin surface, which protects the scar from mechanical damage and

moisture evaporation, thereby restoring the water balance in the epidermis, normalizing the functional activity of fibroblasts and preventing further proliferation of connective tissue [1, 9, 10, 24, 41].

Silicone plates are a highly effective tool; however, its use limits the need for fixation with the help of plasters: since the plate must be worn around the clock for a long time, maceration and inflammation of the skin occur. In addition, the plate cannot be fixed to moving and open parts of the body. A more convenient form of silicone is silicone medical gel [6]. Among the relatively new drugs based on silicone gel, the SIK-A-KEA self-adhesive anti-scar plaster should be noted [1, 10, 44].

The mechanism of action of silicone plates and gels is based on: uniform pressure, which reduces the volume of the extracellular matrix; hydration (hydration) of the rumen; squeezing the capillaries; decreasing the delivery of inflammatory mediators; decrease in collagen synthesis due to oxygen starvation (which contributes to the parallel arrangement of collagen fibers). Currently, the therapeutic effect of silicone gel is associated with occlusive properties and a decrease in water evaporation from the epidermis. Often, silicone gel is used for the prevention of scars as a first-line non-invasive treatment in the early stages of scarring. A pronounced discomfort of the method is the need to wear bandages/plates during the day, as well as the impossibility of their attachment in some anatomical areas (folds, neck, etc.) [6, 17, 45, 46].

Table 4: Application of compression (pressure) dressings in the treatment of scars

	Compression clothing	Silicone plates, plasters and gels	References
Application area	Wearing compression clothing is indicated when there is a threat of the formation of extensive scars after injuries, burns	Non-invasive treatment of post-burn scars and contractures in the early stages of scarring, scar prevention	[2, 6]
Mechanism of action	Compression clothing immobilizes and reduces tissue tension, dosed pressure on the scars causes them to turn pale and soften up to complete smoothing, since they are sewn from special materials according to special patterns in such a way that the pressure on each centimeter of the skin is 25 mm Hg. Art.	Uniform pressure that reduces the volume of the extracellular matrix; hydration (hydration) of the scar; squeezing of capillaries; decreased delivery of inflammatory mediators; decrease in collagen synthesis due to oxygen starvation, (which contributes to the parallel arrangement of collagen fibers)	[1, 2, 6]
Contraindications	Acute or aggravated chronic infectious skin diseases, allergic reactions	persistent postoperative sutures, open wounds, skin	[2]
Complications with long-term use	Exacerbation of concomitant chronic skin diseases, secondary infection, slowing down of regeneration processes in the wound		[2]

Hormone therapy

Hormone therapy of keloid and hypertrophic scars has become widespread in recent decades. It was most often used after surgical treatment. Injections of corticosteroids (diprosan, etc.) reduce collagen synthesis not only by inhibiting fibroblast division, but also by increasing the concentration of collagenase. In addition, steroids have a pronounced anti-inflammatory effect [6]. Intracarceral administration of corticosteroids inhibits the synthesis of inflammatory mediators and fibroblast proliferation, which reduces the formation of glucosaminoglycans and collagen during wound healing [10, 24, 41, 42, 47].

The most common use is hydrocortisone and its analogs in the form of injections, and topical corticosteroid drugs are also widely used, which are applied daily directly to the formation. In the literature, data appeared on the effective clinical use of a corticosteroid–betamethasone dipropionate: injections of diprosan and Belosalik ointment, applied under an occlusive dressing [1, 9]. Hormone therapy is used in three directions: 1) monotherapy (for radical treatment of keloid scars); 2) in combination with other methods (surgery, silicone coatings, etc.); 3) for symptomatic treatment. Complications during hormone therapy are atrophy and pigmentation disorders [3, 6, 48-53].

Enzymatic therapy

For the treatment of pathological skin scars, enzyme preparations (collagenase and hyaluronidase) are also actively used, which provide hydrolysis of collagen and glycosaminoglycans in scar tissue with subsequent restoration of the normal composition and structure of the extracellular matrix [10]. The classic remedies are preparations of the proteolytic enzyme hyaluronidase: Lidase and Ronidase, as well as new ones: Longidase (hyaluronidase with polyoxidonium) and Fermencol [54, 55]. Some researchers recommend combining collagenolytic therapy with compression therapy since the isolated use of collagenases can improve the trophism of scar tissue due to the thinning and destruction of collagen fibers that compress the vessels of the cutaneous plexus [1].

Hyaluronidase breaks down one of the components of the pathological extracellular matrix–hyaluronic acid, which is a cementing substance of connective tissue, and thus: increases tissue

and vascular permeability; facilitates the movement of fluids in intertissue spaces; reduces tissue swelling; softens and flattens scars; prevents the formation of scars. A systemic means of preventing scars is longidase, which combines the enzymatic properties of hyaluronidase and the immunomodulatory properties of polyoxidonium. The area of application of drugs is wide [30, 56]. The analysis of all available works showed that a combination of several methods is most often used. Treatment is considered effective if no relapses occur within two years when the optimal clinical picture is achieved [6].

Pharmacotherapy

The modern arsenal of drugs that are used in the treatment of pathological scars is represented by drugs of various pharmacological groups that affect specific links in the pathogenesis of scar tissue [1, 10, 57-59].

To date, there is information about the advisability of using drugs from the group of cytostatics–5-fluorouracil and bleomycin in the treatment of keloid scars. This method has been proposed as an alternative to steroid injections in difficult-to-treat cases and is under study. Some studies have proven the effectiveness of monotherapy of keloids with 5-fluorouracil (an antimetabolite that inhibits the reproduction of fibroblasts), showing the advantage of using bleomycin in the treatment of large keloid scars compared with the combined use of glucocorticosteroids and cryotherapy [1, 5, 9, 11, 24, 41, 60].

A calcium channel blocker (verapamil) injected into the scar has been shown to be promising in three clinical trials for preventing recurrence after keloid excision. Kovalevsky A. A. *et al.* (2008) showed the effectiveness of phonophoresis with verapamil ointment for the prevention and treatment of hypertrophic and keloid scars in patients with burn injury. The mechanism of action of verapamil is explained by the inhibition of calcium-dependent processes involved in the synthesis of the extracellular matrix, as well as by an increase in its degradation (increased production of collagenases) [61-64].

The use of antihistamines (blockers of H1-histamine receptors) has been proposed as a means of symptomatic therapy that eliminates itching and burning in the keloid area, and in order to model the size of the scar, which is based on the fact that histamine stimulates collagen synthesis, contributing to the formation of a keloid [10].

Among the innovative approaches to the prevention of the formation of pathological scars, the use of cytokine preparations should also be noted. According to modern concepts, the cytokine TGF-beta (transforming growth factor-beta) is one of the leading growth factors in the pathogenesis of keloid formations. TGF-beta1 and TGF-beta2 contribute to the development of pathology, while TGF-beta3, on the contrary, promotes physiological wound healing, which gives prerequisites for the possible use of TGF-beta1 and TGF-beta2 inhibitors and TGF-beta3 inducers in scar therapy [10, 65, 66]. In particular, the results of clinical trials of intradermal administration of the drug Avotermin (recombinant human TGF-beta3) have been published, which indicate its high efficiency in the prevention of pathological scarring [67-69].

Particular attention should be paid to another new and very promising method of treating keloid scars—therapy with interferons, which are also known for antiproliferative properties [1, 5, 10, 13, 24, 70]. It was found that interferon-alpha2b reduces the synthesis of collagen types I and III, the main structural components of keloid tissue. According to the literature, systematic injections of interferon-alpha2b are much more effective than injections of corticosteroids, and when injected into the suture line after excision of the keloid scar, they can prevent its recurrence prophylactically [1, 5, 10, 24, 57, 71].

The use of vitamin A and its derivatives (retinoids) by application to the skin surface or intradermal injections has been proposed as an experimental method of treatment. Retinoids accelerate wound healing, cause regression of abnormal scar tissue, increase epidermal cell proliferation and inhibit fibroblast proliferation and collagen deposition. Thus, the significant efficacy of tretinoin in the form of 0.05% cream was shown in the treatment of keloid and hypertrophic scars in a double-blind, placebo-controlled clinical trial [1, 5, 13, 24, 69, 72].

To normalize the wound healing process, it is possible to use antioxidants—substances whose action is aimed at normalizing lipid peroxidation processes, reducing oxidative stress, improving microcirculation and restoring endothelial function [73].

Thus, the efficacy of topical application of vitamin E for the prevention of keloid formation, as well as improvement of cosmetic results after surgery in children, was established in a prospective controlled study: none of the patients in the experimental group developed a keloid, 96% of patients noted a noticeable cosmetic effect. This effect of tocopherol can be explained by its stabilizing effect on factors leading to the development of endothelial dysfunction, namely, the ability to inhibit lipid peroxidation, stabilize cellular, including lysosomal, endotheliocyte membranes, and suppress inflammatory processes [74].

Plant polyphenols—flavonoids, hydroxycinnamic acids, tannins—are currently recognized as promising antioxidants [75-77]. Some authors noted that quercetin and kaempferol, substances included in onion extract, inhibit the production of collagen and fibronectin by inhibiting the expression of 2, 3, and 4 SMAD genes involved in the realization of signals of the growth factor TGF-beta, thereby affecting the pathogenesis scars [78, 79]. Thus, the use of products containing phytoextracts in which the main biologically active substances are flavonoids, including topical hydrogel-based preparations, is an important component of the treatment of keloids [1, 10, 14, 80].

Prospects for the use of transdermal therapeutic systems

Transdermal therapeutic systems are designed to continuously deliver the medicinal substances contained in them through intact skin into the systemic circulation for a long (limited only by medical indications) time at a predetermined rate. Although the physiological role of the skin is primarily in isolating the internal environment of the body from external influences, in particular from the penetration of xenobiotics, the supply of medicinal substances through the skin in the form of ointments has been known for a long time. However, it is practically impossible to control the rate of delivery of medicinal substances or to carry out a long-term supply of medicinal substances using ointments. Medicated patches are designed to act locally (such as a pepper patch), not to deliver medicinal substances into the systemic circulation. Transdermal therapeutic systems belong to a new generation of dosage forms that

use the technology of controlled release of drugs. It is based on the fact that medicinal substances are continuously supplied to the body at a rate that creates a constant level of concentration of medicinal substances in the bloodstream, close to the minimum therapeutic level. In contrast, the concentration level of drugs when using traditional dosage forms has peaks that can reach toxic levels when side effects occur. Transdermal therapeutic systems turn out to be a very promising method for the treatment and prevention of various diseases, in some cases even being an analogue of a highly effective intravenous drip method of drug administration. Transdermal therapeutic systems provide faster drug exposure compared to oral administration due to their entry directly into the bloodstream [81, 82].

Based on the foregoing, it becomes obvious that starting to develop a fundamentally new structural basis for a transdermal therapeutic system containing the most effective and safe compounds of the regenerating and antioxidant mechanisms of action (vitamins and other biologically active compounds) from the point of view of preventing the formation of keloids. This will help in solving the problem of not only preventing the formation of a keloid in the dermis, but also its subsequent growth and exit to the surface layers of the skin. It should be taken into account that a number of people have various kinds of allergic reactions and other contraindications, as well as the possibility of using transdermal therapeutic systems for patients of different ages. When looking for sources of information about compounds with regenerative and antioxidant effects, it is worth paying special attention to the Scientific Publishing House «Innovare Academic Sciences» (India), in whose journals you can find a large number of materials devoted to phytochemical screening of plants of different classes, for example [83-85], which underlines the leading role of the Indian pharmaceutical industry in the field of pharmacognostic analysis.

CONCLUSION

Modern medicine has achieved significant results in the development of techniques to avoid surgeries. At the same time, surgical methods are still one of the main tools for treating pathologies in the human body. Plastic surgery and cosmetology are gaining popularity every year, and sports injuries require the use of combined treatment methods, but any such intervention leads to the risk of keloids. It is worth noting that the younger the person, the higher the likelihood of developing a keloid due to the high degree of elasticity of the skin at an earlier age, which is prone to scarring than in older people. Also, the risk of developing keloids in women is higher than in men since their skin is more elastic. Thus, it can be stated that children and young women are most at risk of keloid formation, both due to the physiological processes of skin scarring and the preference for plastic surgery, cosmetic procedures, and other methods of correction. In world pharmaceutical practice, there are not enough existing ways to prevent the development of keloid. Modern trends in the development of pharmaceuticals require new approaches to solving this problem. It is necessary to conduct research on the selection of a fundamentally new structural basis for a transdermal therapeutic system containing the most effective and safe compounds of the regenerating and antioxidant mechanisms of action (vitamins and other biologically active compounds) from the point of view of preventing the formation of keloids, which will help in solving the problem of not only preventing the formation of keloids in the dermis, but also its subsequent growth and exit to the surface layers of the skin.

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CONFLICT OF INTERESTS

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