Pattern of filler and Botulinum toxin induced facial Ischemia and prevention of hypertrophic scars and keloids Relying on the points of clinical psychology

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Abstract
Background and purpose: hypertrophic scar is a lesion that is caused by excessive healing of the wound and leaves aesthetic and sometimes functional problems for affected patients and causes physical, mental and change in their quality of life. Nowadays, various methods including surgery It is used to treat these lesions, but due to frequent recurrence, the patient's problems persist.

Materials and methods:
This prospective study was a randomized controlled trial on 40 patients with hypertrophic scars who were referred to the plastic surgery clinic of Waliasr Hospital in Imam Khomeini Hospital Complex (RA). It was done during the year 1402. The findings and results obtained in terms of the relationship between the control group and the study variables were analyzed with SPSS software version 16 and the significance level was considered to be less than 0.05.

Conclusion:
Botulinum toxin type A injection in hypertrophic scar not as an independent method but along with other treatment methods such as surgery can be useful in controlling and improving the symptoms caused by scar.

Introduction

Physical injuries from surgical incisions, burns and infections may cause skin damage and scarring. Most superficial injuries do not leave much scars, but deep skin injuries can cause serious problems in the form of hypertrophic scars and keloids. Hypertrophic scars and keloids are disorders caused by the excessive growth of fibrotic tissue, which causes the tissue to bulge (1). These conditions occur due to abnormal wound healing. At first, it is red and itchy, but these symptoms may gradually improve. These two types of scars have differences; In the hypertrophic type, the scar is limited to the borders of the initial injury and after one or two years it becomes smaller, but in the keloid type (meaning crab claw in Greek), the scar extends beyond the damaged tissue and does not regress, so to speak. That extra flesh is said to differentiate these two types after the necessary time has passed (2). Hypertrophic scars and keloids, in addition to cosmetic problems, can cause functional impairment due to tissue shrinkage and subjective symptoms such as itching (3). Hypertrophic scar and keloid are basically a type of abnormal repair response to injury that are caused due to disruption of the normal repair response. Keloid is a raised, erythematous, hard and fibrotic lesion that is in the soft area, ear, neck, chin, front part of sternum, upper back, upper Arm and lower leg is common (4) and is often accompanied by itching, burning or pain, and it grows and spreads beyond the initial wound; While the hypertrophic scar remains limited to the original wound area and regresses over time (5). The probability of keloid recurrence after surgery is much higher than that of hypertrophic scar. The age group with the highest prevalence of keloid is between 10-30 years old, that is, when teenagers or young people give the most importance to their appearance. Keloids are more common in Asians and Africans, especially those with darker skin (Fitzpatrick classification IV and above) (6). Hypertrophic scar is the result of increased activity of fibroblasts in the

healing of skin wounds. Lesions may be painful or itchy and may cause a burning sensation. Hypertrophic scars are less than 1 cm in size, while larger lesions, which usually leave the edge of the wound, are called keloids. These lesions are found in people with dark skin and in African and Asian races are up to fifteen times more common (7). Genetically, they have an autosomal dominant pattern with incomplete penetrance. Histologically, the thickness of the epidermis increases. The deposition of collagen and glycoproteins increases and the collagen fibers are bigger and thicker than normal and parallel to the epithelium. Fibroblast proliferation is usually normal, but their ability to produce collagen is twenty times that of normal fibroblasts (8). These cells respond to lower concentrations of beta-type growth-modifying substance (TGF-B). These lesions have an unpleasant appearance and cause concern for affected patients, so the treatment goals include removing symptoms, returning function to the affected area, and preventing recurrence. Since the underlying mechanisms causing hypertrophic scars are not yet fully understood, many treatment measures are not associated with high success (9). Keloids and hypertrophic scars are the result of benign proliferation of skin collagens. Patients with these skin lesions often experience physical disorders (deformity, movement restriction, pain and itching, and psychological problems (cosmetic concerns) (10). Although the basis of the formation of keloid and hypertrophic scars has not been fully determined. It is assumed that that these lesions are caused by the increase in collagen production by fibroblasts compared to normal fibroblasts (3), therefore, suppressing the uncontrollable activity of fibroblasts in keloid lesions and hypertrophic scars may be necessary in therapeutic approaches to abnormal response, damages (4) Also, there is an increase in vascular tissue in keloids and hypertrophic scars (11). - TGF (Transforming growth factor-beta) plays a role in the pathogenesis of keloids. For many years, many treatments have been used for keloid, including intralesional steroid injection, cryotherapy, pressure dressings and silicone gels and fluorouracil (Fluorouracil=5-FU-5), interferon radiotherapy and finally surgery, but it is still a definitive and accepted treatment. There is no cure for this lesion and the recurrence rate after treatment is very high (12). For definitive and effective treatment of this lesion, it is necessary to acquire detailed knowledge about its pathogenesis. One of the mechanisms that has recently attracted the attention of researchers is the disruption of the Hedgehog messenger pathway and the genes of this pathway, including Gli1, which has been proposed since 2001. By examining 5 keloid samples, Kim et al showed that Gli-1 oncogene is abundantly expressed in keloid. (13) Gli1 oncogene, which was first discovered in glioma, is involved in the pathogenesis of basal cell carcinoma (BCC). Many types of brain tumors, some sarcomas and other types of tumors are involved.

Common treatment strategies for hypertrophic scars and keloids include:

First lines of prevention and treatment (non-invasive methods): silicone sheets, radiotherapy, corticosteroids, fluorouracil.

Second lines of prevention and treatment (semi-invasive and invasive methods): cryotherapy, laser therapy, surgery

New studies in the field of prevention and treatment: imitation of scarless healing in the fetus, treatment with mesenchymal stem cells, use of tissue engineering, botulinum toxin A, bleomycin, transforming growth factor beta.

In the following, we will explain each of the treatment and prevention strategies in detail. The current study was conducted with the aim of the latest algorithms for the treatment and prevention of hypertrophic and keloid scars, relying on the points of clinical psychology.

Method

This prospective study was a randomized clinical trial with a control group that was conducted on 40 patients with hypertrophic scars who were referred to the plastic surgery clinic of Waliasr Hospital in Imam Khomeini (RA) hospital complex during the year 1402. Became. In each patient, the lesion was randomly divided into two parts. Randomization was done based on the block of four numbers closed by Excel software (MS Office Excel, Microsoft Corp., USA). Importer Darian (drug with a concentration of 200 units per milliliter with a dose of 8 units per cubic centimeter of the lesion and in the other part of the lesion of the group) (second, injection of normal saline with the same volume was performed. Injection solution of normal saline or botulinum toxin type A in syringes The same was prepared by the supervisor. Each syringe and part of the lesion was given a code that only the supervisor knew about and the researcher and the patient did not know about the contents of the syringes. The injection was repeated at intervals of one month and up to three times.Patients were evaluated 9 months after the last injection by three plastic surgeons who did not know the type of injected substance, based on the Vancouver criteria. In the Vancouver criteria, lesion color is 0 to 2, vascular status is from 0 to 3, size is from 0 to 3. And gives points from 0 to 5 to the consistency of the lesion. Zero is the normal state and a higher number indicates a greater distance from the normal state. Inclusion criteria for patients with hypertrophic scars, age over 12 years, patients with consent to participate in the study with knowledge of its conditions and complications, and exclusion criteria also include the patient's lack of consent to perform a research intervention, sensitivity to botulinum toxin A, pregnant women and , nursing patients

with neuro-muscular diseases and any contraindications to the use of Botox, such as infection. Was taken. Photography and other stages of intervention and research were done for free for the patients. The findings and results obtained in terms of the relationship between the control group and the study variables were analyzed with SPSS software version 16 and the level of significance It was considered smaller than 0.05.

Discuss

The first phase of wound healing is the inflammatory phase that begins immediately after the tissue injury and continues for approximately two to three days after the injury. Coagulation cascades, complement activation and platelet degranulation through the formation of platelet clusters and fibrin matrix prevent further loss of fluids and blood. The immune system and inflammatory reactions are activated to prevent infection and collect dead tissues. Neutrophils and then macrophages first migrate to the wound site using chemotaxis factors produced by platelets and bacteria. In this phase, platelet degranulation causes the release and activation of transforming growth factor (TGF), especially TGE 1-2, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1), and epidermal growth factor (EGF) (11,12).

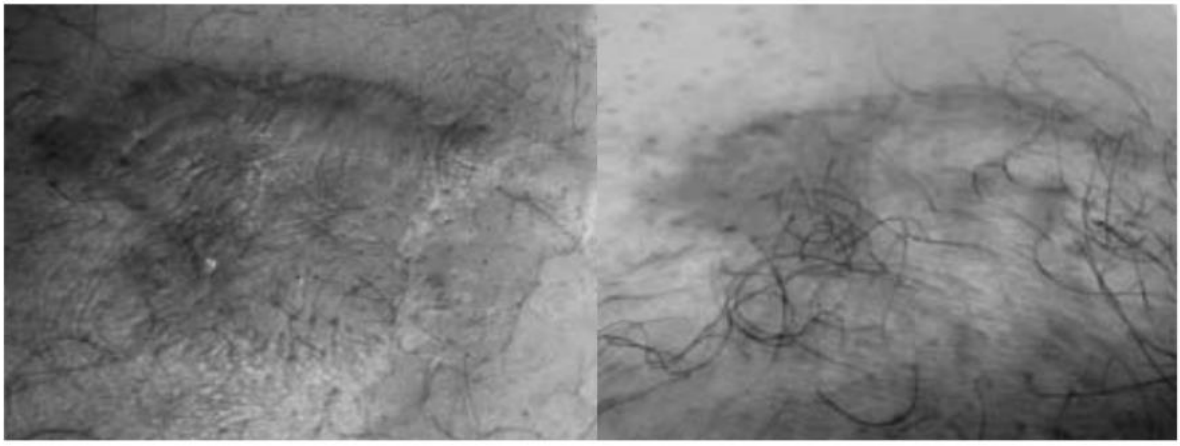

Fig 1. A 27-year-old man with scars on the external surface of the left thigh before the intervention and on the right side after the intervention. Reduction of pigmentation in the right half of the lesion in the botulinum toxin type A injection area.

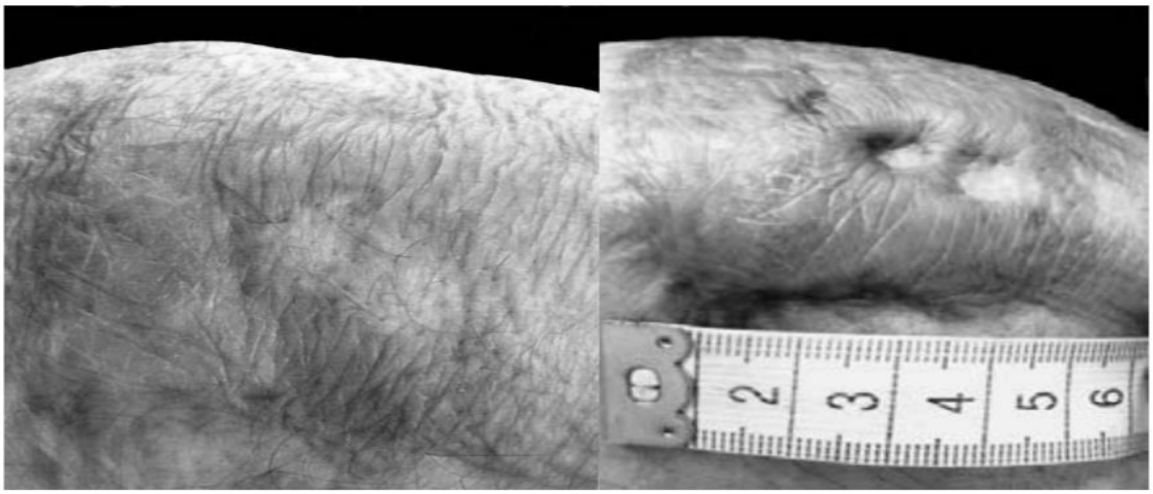

Fig 2.A 24-year-old man with a scar on the right left knee before the left side depigmentation intervention In the area of botulinum toxin type A injection in the lower half of the lesion.

Vascular endothelial growth factor (VEGF) produced by epidermal cells is a positive regulator of angiogenesis. Due to this problem, overexpression of VEGF gene is related to excessive formation of capillaries, type 1 collagen production and overall increase in scar. The amount of periostin in hypertrophic scars and keloids is abnormally high compared to normal findings. Therefore, periostin can also be considered as a target factor for the prevention of hypertrophic scars and keloids. Hypertrophic scar is formed as a result of excessive healing of the wound and usually occurs four weeks after skin damage (13). If the epithelialization lasts more than 21 days, the possibility of hypertrophic scar formation increases, which usually remains in the area of the wound. The occurrence of TGF-B The response rate of fibroblasts to it and the amount of insulin-like growth factor 1 increase in these 1 and 2 lesions, and in the hypertrophic scar, there are more Langerhans cells, T lymphocytes and mast cells than in normal tissues. However, due to the effect of various factors on wound healing, there is still no solution for the complete treatment of hypertrophic scars, and current treatment methods have many (14).

The first lines of prevention and treatment are non-invasive methods

Silicone sheets: Although the results of using silicone gels or sheets are contradictory, currently silicone products are considered the first line of treatment and prevention of hypertrophic scars and keloids. Various products of silicone are currently available and used, including gel sheets and silicone spray. As a barrier to protect the wound and increase hydration, this factor prevents the proliferation of fibroblasts, as a result, it prevents the formation of scars by reducing collagen. In a research that was conducted for the use of silicone gel on the scars of patients with hypertrophic scars and 2 with keloid scars, 90% of them had a significant improvement in the appearance of the scar. This improvement was accompanied by a significant reduction in the red color of the scars and the size of the scars. Although the elasticity of skin hydration and evaporation of skin moisture were not significantly changed.Given the contradictions about the effectiveness of silicone gel on hypertrophic scars and keloids, a new systemic research shows that silicone gel and silicone gel sheets in preventing From keloid or hypertrophic wounds, it is especially effective in skin (15).

Radiotherapy: Several studies have shown the effectiveness of radiotherapy for the treatment of keloids. Radiotherapy has been used and studied in the treatment of keloid, both as an external beam treatment method and as an internal radiation treatment method (brachytherapy). Radiotherapy is generally performed as an adjunctive treatment 24 to 48 hours after scar correction surgery, and in the recommended 40 Gy radiation in several sessions, the proposed mechanism of radiotherapy for keloid treatment is through inhibition of vascularization followed by anti-fibroblast activity. Suppression of angiogenesis reduces the sending of inflammatory cytokines, and successive inhibition of fibroblast activity leads to a decrease in collagen synthesis, thus preventing the formation of keloids. Thyroid and breast should be treated with great caution after obtaining informed consent from the patient. Shen et al reported that the recurrence rate was 9.59%. Recently, radioactive skin patches have been used for localized skin diseases such as skin cancer and keloid. Radioactive skin patches use different types of radioactive isotopes and have variable effectiveness for treating keloid. These patches are often used in combination with other treatment (16).

Corticosteroids: Steroid injection into the lesion, steroid strips or adhesives and steroid ointments have been used in the treatment of hypertrophic scars and keloids. The most common way to administer steroids is to inject them into the lesion, although steroid strips or stickers are gradually becoming more common. The mechanism of this treatment method is attributed to its anti-inflammatory effects (17). In addition, steroid treatment seems to reduce collagen synthesis, glycosaminoglycan production, fibroblast proliferation, and collagen and fibroblast degeneration. Another proposed mechanism is the induction of vasoconstriction by local steroid binding to classical glucocorticoid receptors. Keloids treated with intralesional steroid injections vary and are reported between 50 and 100%, and the recurrence rate is reported as 9 to 50%. Most previous studies have used triamcinolone acetonide (TAC) alone or in combination with other therapies, such as fluorouracil (FU-5), verapamil (a calcium channel blocker), cryotherapy, or (18). Injections range from 10 to 40 mg/mL, but the recommended concentration of TAC in a single treatment is 40 mg/mL for keloid healing. Injections are given once to twice a month until the scar is flattened. Intralesional steroid injections are possible. It has side effects such as skin atrophy. Fluorouracil FU- is a pyrimidine analog, so it disrupts DNA replication and is mainly used to treat cancer. By injecting it into a vein, it can be used to treat cancer, esophagus, stomach, pancreas, colon, breast, and cervix. In addition, this drug has been used to treat keloid. The possible mechanism of its effect is through inhibition of angiogenesis, inhibition of fibroblast proliferation, and inhibition of collagen type 2 expression. 1 is induced by the effect of TGF-, this treatment is used alone or in combination with other treatments, and the preferred method and its use is intralesional injection. Nanda colleagues have reported that in most of the patients for whom FU- was injected into the lesion weekly for 12 weeks with a concentration of 50 mg/mL, the size of the scar decreased, its possible side effects include pain and ulceration (19).

Second lines of prevention and treatment of semi-invasive or invasive methods

Cryotherapy: Cryotherapy has been used to treat hypertrophic scars and keloids as a single treatment or in addition to other treatments such as steroid injection into the lesion. Treatments in which cryotherapy and triamcinolone injection into the lesion are combined together, hypertrophic scars and Improves keloids significantly. The delivery method for cryotherapy is variable and includes contact spray and intralesional needle probe method. In the intralesional needle probe method, better results are observed than the spray or contact method and it causes rapid re-epithelialization. The proposed mechanism in cryotherapy is tissue necrosis due to vascular damage. It appears that necrotic tissue caused by frostbite (as opposed to burn injury) induces the release of unique inflammatory cytokines; Therefore, the response of fibroblasts may be different. The success rate of cryotherapy after multiple sessions varies between 32 and 74%.

laser therapy: Laser therapy was used to treat keloids in the 1980s, and several types of lasers with different wavelengths were investigated and reported. Among them, the most commonly used laser to treat hypertrophic scars and keloids is the pulsed dye laser (PDL) (585 nm). Laser treatments vaporize blood vessels. By doing this, inflammatory cytokines are limited in their ability to reach to hypertrophic scars and keloids, thereby reducing the occurrence of misplaced scars. Potential side effects of laser therapy include hyperpigmentation, hypopigmentation, blister formation, and postoperative itching. Surgical resection is a traditional treatment method for hypertrophic scars and keloids. The maturation and regeneration phase of classical wound healing may take more than a year; therefore, the removal of hypertrophic scars and keloids should be considered at least one year after the initial wound treatment. Over time, hypertrophic scars generally regress naturally or with treatments. Non-invasive, such as steroid injections, heal to some extent, therefore, in many cases, there is no need to perform scar correction surgery. In the case of keloids, surgical removal alone often leads to disappointing results. (20) To improve the outcome after surgery, multi-method combined treatments, such as steroid use after surgery or radiotherapy, can be added to it. When surgeons perform scar correction surgery, they must provide tension-free closure of the wound, until the tension-induced inflammation is reduced and, in this way, recurrence is prevented. Various techniques, such as three-layer sutures and The tension reducer in the fascia and under the Z plastic cover or local flap reconstruction can be done depending on the patient's condition 61 and 60, the recurrence rate of hypertrophic scars after scar correction surgery is low, but the recurrence rate of keloids after scar correction surgery is 45-100%. Scar correction is not. In the case of keloids, surgical removal alone often leads to disappointing (21). To improve the outcome after surgery, multi-method combined treatments, such as steroid use after surgery or radiotherapy, can be added to it. When surgeons perform scar correction surgery, they must provide tension-free closure of the wound, until the tension-induced inflammation is reduced and, in this way, recurrence is prevented. Various techniques, such as three-layer sutures and The tension reducer in the fascia and under the Z plastic cover or local flap reconstruction can be done depending on the patient's condition 61 and 60, the recurrence rate of hypertrophic scars after scar correction surgery is low, but the recurrence rate of keloids after scar correction surgery is 45-100%.

Using new studies in the field of prevention and treatment

Imitation of scarless healing in the fetus

Surgical incisions in mammalian embryos heal rapidly without scarring and are almost indistinguishable from undamaged tissue. In 1979, the same observation was also reported in human embryos. An initial hypothesis was that factors such as complete sterility, amniotic fluid richness in growth factors, and low oxygen pressure were responsible for scar-free healing in the fetus. However, subsequent studies have shown that the presence of these factors is not sufficient for scar-free healing. Current efforts are aimed at identifying factors intrinsic to fetal tissue that enable scar-free healing. Basically, the study of fetal wound healing is difficult because the fetus grows and develops in the closed and protective environment of the uterus, so animal fetal models are widely used. Initial studies in the field of fetal wound healing have several histological and chemical differences. Has shown between the healing wounds of fetuses and adults. Fetal wound healing has a much lower number of inflammatory cells than adult wounds.The absence of these cells probably causes a very different microscopic environment in terms of the appearance of cytokines and growth factors, and this may affect the action of fibroblasts in the production of ECM molecules with a normal renewal pattern and not with a scar pattern. Hyaluronic acid in wounds Embryonic cells are present in much higher concentrations, and the ECM molecule fibronectin is produced rapidly (22). These molecules probably react with the cells involved in healing and may enhance the regeneration phenotype. Also, there is a higher level of matrix metalloproteinase activity in fetal wounds, which may allow early maturation and regeneration of skin wounds and scar collagen. Fibroblasts produce ECM molecules, whose configuration is one of the important elements in the creation of regenerated tissue or scar tissue, so it is possible that changes in the population of

fibroblasts or the phenotype of fibroblasts in the wound play an important role in the loss of healing without a scar. Laboratory studies show that Fetal fibroblasts express more collagen 3 and 4 compared to adult fibroblasts (23).

Treatment with mesenchymal stem cells: Mesenchymal stem cells (MSC) have immune regulatory and anti-fibrosis effects through the secretion of paracrine growth factors. The anti-fibrosis effects of these cells have been investigated and reported in fibrotic diseases such as myocardial infarction, kidney fibrosis, and liver cirrhosis. Also, MSC can be used to prevent or mitigate excessive inflammatory processes that are characteristic of hypertrophic scars and keloids. MSC treatment has different administration methods and doses. The method of use is through systemic injection, local injection at the wound site into the dermis or subcutaneously or through a scaffold impregnated with MSC. The possible mechanisms of MSC treatment include changing and inhibiting the activity of cells that exacerbate inflammation, anti-fibrosis activity by inhibiting the differentiation of myofibroblasts and the production of type 1 and 3 collagens and promoting normal angiogenic activity that contributes to normal wound healing. Although many researchers have reported anti-inflammatory and anti-fibrosis effects for MSC, there are also reports of a possible anti-inflammatory effect of MSC (24). For this reason, it is necessary to carry out long-term research studies and pre-clinical studies using this method in clinical practice

Table 1. Distribution of the frequency of different underlying causes of keloid in the patients under investigation

underlying cause	Number	Percent
trauma	9	56/25
surgery	4	25
ear piercing	3	18/75
tattoo	1	6/25
Accidental injury	1	6/25
acne	3	18/75
Spontaneous keloid	4	25
Total	28	100

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Using tissue engineering: Numerous researches are being conducted on the use of biopolymers and engineered tissues. As an example, injectable hyaluronic acid hydrogels have been used to heal wounds and scars, which resulted in a significant reduction in fibrosis and scar formation in a rabbit model wound. Apligraf is the first two-layer engineered skin approved by the US Food and Drug Administration. (FDA) approved. This engineered skin was cultured with embryonic cells with the goal of producing scar-free wound healing like an embryo. Our research on fully decellularized human skin showed that the basement membrane is the most attractive for the cells added on the scaffold. The structure of the basement membrane is different between keloids, hypertrophic scars and normal skin, and the abnormal structure of the basement membrane can cause the proliferation of keratinocytes in the epidermis of wounds. become hypertrophic Studies on scarring have mainly focused on the role of fibroblasts, and our information on the role of keratinocytes is very limited. Evidence shows that keratinocytes can play an important role in pathological fibrosis through paracrine regulation of fibroblasts. Also, keratinocytes obtained from scar tissues have different gene expression than normal keratinocytes. After skin damage, the basement membrane acts as a structural scaffold that can attract epidermal progenitor cells and also cause the activation and migration of keratinocytes (25). It maintains the balance between keratinocyte regeneration and differentiation during wound healing and regeneration. The clinical results of skin autographs for facial wounds showed that this scaffold improved the scar. In this method of treatment, faster growth, proliferation of blood vessels and migration of epithelial cells have been observed in wounds. Although this method still did not completely remove the scar.

Botulinum toxin A

Botulinum toxin, derived from Clostridium botulinum, is a powerful neurotoxin that blocks neuromuscular transmission. Some authors have reported that botulinum toxin type A can reduce muscle tension during wound healing by reducing muscle tension. Minimize the scar, which causes the fibroblast cell cycle to stop in the non-proliferative state of G0 or G1, and 78 and 77 also affect the expression of TGF-1.

Bleomycin

Bleomycin is an anticancer, antiviral, and antibacterial cytotoxic agent obtained from Streptomyces verticillus and has been used to treat skin diseases such as warts. This agent has also been used for hypertrophic and keloid (26). Several studies have shown that human dermal fibroblasts in bleomycin treatment, even with the simultaneous presence of 1-TFG, show a decrease in collagen synthesis and a decrease in the level of the enzyme lysyl oxidase, which plays a role in collagen maturation. In addition,

bleomycin treatment induces apoptosis. The method of using it is as an injection into the lesion, and 1.5 IU/mL of bleomycin is injected in two to six sessions at intervals of one month. Several studies have reported that in patients with keloid, complete smoothing of the lesion was observed and other symptoms such as itching and pain were also resolved. Its possible side effects included pain at the injection site and hyperpigmentation, but the side effects of systemic Aloe 80 were not (27).

Conclusion

Hypertrophic scars and keloids are caused by abnormal wound healing. Excessive production of ECM is one of the characteristics of these lesions. An increase in inflammatory and proliferative processes and a decrease in maturation and regeneration processes cause excessive production of ECM. Genetic and systemic factors are also related to these excessive scar lesions. Although encouraging results of molecular and cytokine therapies are still regularly reported, current strategies for prevention and treatment are still mainly focused on reducing inflammatory processes. A better understanding of the mechanisms causing excessive scarring is necessary for the development of effective methods and strategies in prevention and treatment.

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