STRATEGIES IN THE TREATMENT OF KELOID AND HYPERTROPHIC SCARS

Dražen Shejbal, Vladimir Bedeković, Mirko Ivkić, Livije Kalogjera, Zorica Alerić and Petar Drviš

University Department of ENT and Head and Neck Surgery, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Keloids and hypertrophic scars are the consequence of excessive collagen deposition during the process of wound healing. The increasing number of operations and injuries, the widely accepted culture of piercing, and higher cosmetic criteria have led to a greater interest in the methods of their treatment. Due to the lack of an appropriate animal model, the respective research is based solely on clinical experience. A great number of therapeutic options indicates that no ideal therapy has yet been found. Use of multiple modalities is often necessary to treat the lesions successfully. The molecular, biochemical and clinical features of keloids and hypertrophic scars as well as treatment modalities are discussed.

Key words: *Cicatrix hypertrophic – therapy; Cicatrix hypertrophic – physiopathology; Keloid – therapy; Keloid – etiology; Wound healing – physiopathology; Postoperative complications – therapy*

Introduction

Wound healing is a process that may result in either scar or keloid formation. Ideally, wound healing without scar formation can be seen in humans in certain periods of intrauterine development, at about 24th week of gestational age. Disturbances in the mechanisms of the intrauterine fetal wound process of scar development may start in this period to be stopped later on, thus opening new perspectives for investigation[1]. Keloids and hypertrophic scars exclusively affect homo sapiens, and that is why no experiments are possible in an animal model[2]. The increasing number of surgical procedures and injuries, the higher cosmetic criteria, and especially the widely accepted culture of piercing are causes of the higher incidence and increased interest in keloids and hypertrophic scars[3-5]. Keloids can be caused by a minor skin wound such as acne or even a mosquito bite.

Correspondence to: *Dražen Shejbal, M.D., M.S.*, University Department of ENT and Head and Neck Surgery, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: dr.azen@vip.hr

Received August ??, 2004, accepted December ??, 2004

Epidemiology

Keloids and hypertrophic scars mostly affect persons betwen 10 and 30 years of age[6], sex distribution is 1:1, and the incidence ranges from 4.5% to 16%[7]. The incidence in Blacks and Asians is 15-fold that in Caucasians[8]. A family history is also important. The spontaneous development of multiple keloids has been recognized in syndromes such as Rubinstein-Taybi syndrome. A predisposition for keloid formation has been noted in individuals with human leukocyte antigen (HLA) B 14, BW 16 and blood group A[2].

Physiology of Wound Healing

There are several phases in the normal wound healing process[9]. In stage I, or hemostasis, some factors released from alpha platelet granules can increase scarring formation. These factors are the cytokines transforming growth factor-ß (TGF-ß), fibroblast growth factor 2 (FGF-2) and epidermal growth factor (EGF). TGF-ß is the most potent and best investigated scar factor. There are three isomers; isomers 1 and 2 act as scarring promoters, whereas isomer 3 has an opposite action. Higher levels of TGF-ß 1 and 2 are found in hypertrophic scar and keloid[10].

The inflammatory phase is marked with a higher vascular permeability and migration of inflammatory cells. A

prolonged inflammatory phase leads to a bigger scar. In a fetal wound which heals without a scar, this stage is just indicated, mainly without cell infiltration and supported by TGF-ß[11]. Mastocytes that appear in the transitory phase from vasoconstriction to vasodilatation are normally increased in the wound until 3rd week of the injury, whereafter their number decreases. Hypertrophic scars and keloids have a continuously higher level of mastocytes. In pathologic conditions such as hypertrophic scar, scleroderma and keloid tissue mastocytes lead to an increase in the level of interleukin-4 (IL-4), which in turn entails a greater collagen production by direct fibrocyte stimulation, and decreases the concentration of antithrombotic factors tumor necrosis factor-alpha (TNF-a), (IL-1) and IL-6[10,12,13]. At about 7th day of wound healing, inflammatory cells are being replaced by fibroblasts, which are present in a heterogeneous population. This is the migratory phase. Local hypoxia, acidosis, increased histamine level and reduced nitric oxide level help activate clonus with an increased mytotic activity and a higher production of collagen, which results in higher scarring, starting from the stage of protein synthesis, mainly collagen. The increase in oxygen level in the air does not stop this process, which suggests microvascular occlusion[2].

Collagen remodelling commonly starts at about third week, when the process of collagen decay gradually becomes superior to the process of synthesis. The most important factors of collagen decay are interferon gamma, TNF-a and metalloproteinase, and the above mentioned TGF-ß as a counter-factor present throughout the process of wound healing[9,14]. One week of the injury the firmness of the skin is about 3%, at three weeks about 20% and at three months about 80% of the normal skin firmness, and the process of remodelling and healing is completed at about one year of the injury. The scar will never gain the firmness and elasticity of the normal skin[9].

Histologic and Biochemical Characteristics of Keloids and Hypertrophic Scars

Excessive collagen growth is common in both processes. Deposits of collagen and keloids are chaotically distributed in different directions surrounded by a mucinous extracellular matrix with an abundance of eosinophil nodules. These nodules consist of a dense mass of fibroblasts within the collagen, encircled by numerous small vessels with obstructed lumina.

Collagen and hypertrophic scars do not show such a chaotic distribution, their bundles being dense and parallel to the epidermis. Eosinophilic nodules and extracellular matrix are not observed. Obstructed blood vessels are present, however, in a smaller amount than in keloids. Eosinophils, plasma cells, lymphocytes, foreign body cells and mastocytes are common in both processes. The concentration of proline hydroxylase, an enzyme important for collagen production, is approximately 20 times greater in keloid than in hypertrophic scar, thus proving an unlimited collagen production. Even though the inhibitors of collagen, collagenase a_2-macroglobulin and a_2-antitrypsin, are present in the wound, they cannot reduce the higher collagen production. Decorin, a protein molecule that has an impact on TGF-ß neutralization, is in keloid reduced to 25% of the normal value found in a normal scar[2]. Hypertrophic scar, in contrast to keloid, contains special fibrocytes with alpha actin myofibrils, which are important factors in scar contraction[15].

The role of hypoxia and reduction of nitric oxide concentration with consequential local tissue metabolic anomalies could be a trigger for the development of keloid[2].

Classification

The most widely used system is the Vancouver Scar Scale[16]: 1) mature scar – a light-colored, flat or slightly elevated scar; 2) immature scar – a red-colored, sometimes itchy or painful, elevated scar in the process of remodelling; de-elevating tendency; with time it may assume pigmentation of the surrounding skin or can be a bit paler or slightly darker; 3) linear hypertrophic scar (traumatic/surgical) – red, elevated, sometimes itchy within the range of former incision. It can increase in size rapidly for 3 to 6 months and then, after a static phase, begins to regress. The full maturation process may take up to 2 years; 4) widespread hypertrophic scar – usually occurs after burn injury, elevated, with irregular edges, itchy, and can result in contraction; 5) minor keloid – its main characteristic is extension over normal tissue. It can develop up to 1 year after the initial injury, and does not regress on its own. Recurrence often occurs after surgical excision; and 6) major keloid – larger than half a centimeter, develops through years with itching and pain. It has characteristics of new tissue formation.

Some regions of the body have an increased susceptibility to keloid formation. Sporadic cases were presented on mucosa and cornea. The regions with highest potential for hypertrophic scar and keloid formation are presternal region, superior back of the trunk and posterior region of the neck. Ears, deltoid region, thoracic region and beard

Table1. Characteristics of keloids and hypertrophic scars

Characteristic	Keloid	Hypertrophic scar
Incidence	Possible development months after injury	Weeks after injury
Borders	Confined to primary wound	Crosses borders of initial wound
Contraction	No	Possible
Regression	No	Often after 1 to 2 years
Itching and redness	Present	Present
Size	Mostly greater than primary wound	Correlates with wound size
Response to surgery	Mostly recurring	Good, especially with additional therapy

are less affected. Keloids are very rarely seen on palms, scrotum and upper palpebra[17].

Hypertrophic scars are often seen if injury affects reticular dermis or even deeper layers equivalent to burns of second and third degree. Often affected areas are around joints and sites where skin folds meet at a 90-degree angle. Keloids tend to have an irregular surface, and hypertrophic scars are usually smooth[18].

Therapy for Keloids and Hypertrophic Scars

Ideal therapy would directly affect biochemical processes of wound healing, leading the cells of wound edges to form normal tissue, or making the formerly formed scar to transform into the normal tissue, which can be achieved by increasing the levels of FGF, EGF, IF-gamma and TGF-ß 3, or by suppression of TGF-ß 1 and 2[19,20]. Gene therapy can affect the concentration of TGF-ß as well as copper III peptide and tamoxifen[11,21]. With artificial skin replacement placed on the excised scar covered with ultra-thin skin graft for several weeks, appropriate healing of donor and recipient sites can be achieved[22]. TGF-ß can also be affected by antibodies. Previously mentioned methods are still being investigated. Thus, the existing therapeutic options will be briefly presented.

Surgery

Surgery is one of the oldest method of treatment for keloids. Unfortunately, if it is the only method of treatment, the rate of recurrence is about 80%. Rearrangement of the scar parallel to the skin lines (w, z) can be used when the scar or keloid is not big. If a full-thickness skin graft is needed, sutures should be situated without tension. Donor site should be taken from the region of the lowest scar tissue formation potential. The formation of hematoma, seroma and infection should be reduced to a minimum.

Surgery should not be the only method of treatment but should be combined with at least one, potentially two therapeutic options, mostly with intralesional corticosteroid injections[15].

The latest surgical procedure is called "keloid core excision". Epidermis of the keloid with a surrounding thin layer of dermis is separated from the core of the keloid and used as a skin flap that is sutured to the defect. The authors achieved a satisfactory cosmetic effect with a minimal number of complications and low recurrence rate in a series of 24 patients[23].

Radiotherapy

Oncologic complications are the main contraindication for the use of radiotherapy in the treatment of benign lesions that do not compromise life. Radiotherapy alone has low efficacy in the treatment of keloids, and in combination with surgical techniques the success rate is 80%, the same as with corticosteroid injection therapy. If radiotherapy is applied, the first dose is given immediately after the surgery, and the rest of doses are administered over the next few days. Total dosage ranges between 1500 and 2000 rads[24,25]. Iridium 192 in a dose of 14 to 20 Gy can be interstitially apllied[26]. Radiation destroys fibroblasts in the wound, prevents neovascularization, which ultimately leads to a decreased production of collagen. Hyperpigmentation of the skin and carcinogeneic effect are side effects of this therapy[15].

Pressure therapy

It can be used in the treatment of keloids and in the prevention of hypertrophic scar formation after burn injury. A pressure of 18-24 mm Hg is applied for 23 hours and a half of it daily for 6 to 12 months. Ear rings specially constructed for the treatment of keloids in ear lobes can be prescribed in the USA. A specially constructed implant for mouth angles or masks for the whole face, which are car-

ried for a year, are the tools used for the prevention of microstoma and hypertrophic scars of the face after burn injury. Pressotherapy tapes can be applied. Low patient compliance is a major disadvantage of this method.

The postulated mechanims are stabilization of mastocytes, fibroblast degeneration, decrease of cellular infiltration because of hypoxia, and especially effect on a_2-macroglobulin, a decrease of which leads to greater collagen degradation[27,28].

Silicone gel therapy

A 3.5-mm thin semiocclusive soft covering or occlusive blister with a cream is applied. The efficacy of this therapy in combination with some other method is about 80%. Because of easy application it may be especially useful in children. It is applied over at least 12 hours daily for six months. It relieves itching and pain, and is not absorbed through the skin. The mechanism of action is scar hydration. Evaporation is decreased by 50%, which is assumed to decrease capillary activity, also reducing collagen deposition and concentration or proinflammatory cytokines. The only side effect is sensitization[29,30].

Laser therapy

Considering carbon-dioxide laser treatment, best results are achieved by use of the scanning spiral mode of undisturbed flow with less than 1 millisecond tissue exposure time. In this way tissue vaporization is achieved with the least possible coagulation[31]. The 585-nm pulsed dye argon laser produces energy of 6.0 to 7.0 K/cm^2. It is assumed that laser coagulates capillaries causing local hypoxia, releasing lactic acids, and decreasing pH and a_2-macroglobulin concentration, thus enhancing collagenolysis[32,33].

The treatment lasts for about a year. If a fresh wound is treated, laser promotes normal healing and regression of unfavorable effects. Satisfactory results are achieved in about 75% of scars. Side effects include erythema and, in the treatment of grafts, hypopigmentation[34].

Corticosteroids

Corticosteroids have been established as adjuvant therapy to surgery, and can be used in conjunction with other treatment modalities. Intralesional corticosteroid injections alone will improve but not eliminate a keloid[15]. There are several different steroid preparations including hydrocortisone acetate, methylprednisolone acetate and dexamethasone. Triamcinolone is most popular and can be combined with 5-fluorouracil (50 mg/ml 5-FU in 10 mg/ml triamcinolone acetonide). Success rate is about 70%[35]. If applied on the face, the concentration of triamcinolone should be from 2.5 to 20 mg/ml, and for the rest of the body between 20 and 40 mg/ml. Corticosteroids have an inhibitory effect on fibroblast growth and $a_2$macroglobulin, which results in collagen degradation[36]. Pain is the main cause of poor patient compliance. Infiltration anesthesia or EMLA anesthesia (eutectic mixture of lignocaine and prilocaine) should be a standard procedure when corticosteroids are intralesionally applied. Other side effects include atrophy, depigmentation and telangiectasia formation[15,37].

Cryosurgery (cryotherapy)

In most cases, cells and microcirculation are directly destroyed by freezing with the use of liquid nitrogen. Treatment usually includes 2 to 3 freezing cycles lasting from 10 to 30 seconds. Generally, 10 treatments applied 10 to 20 days apart are required. Success rate ranges from 50% to 70% if used as sole therapy, whereas in combination with corticosteroid treatment the success rate exceeds 80%[38].

The disadvantages of cryosurgery include prolonged therapy and recovery period. Melanocytes are very sensitive to freezing, which can induce hypopigmentation in dark-skinned individuals[39].

Interferon therapy

Interferon therapy is the latest therapeutic option. It can be used as sole therapy to induce keloid regression, or can be used after surgical therapy. It is very efficacious in more than 85% of cases. Therapeutic option is intralesional injection of 10 to 200 mcg two times a week during a 4-week period[40,41]. Pain is one of severe side effects, and therefore regional anesthesia may sometimes be required. A flu-like syndrome can be seen but it subsides in two days after the application[2]. Imiquimode is an immunostimulator that can be applied as an ointment to increase endogenous interferon production[42].

Conclusion

Multiple therapeutic options in the treatment of keloids and hypertrophic scars show that no ideal therapy has been found so far. The lack of an animal keloid model is the major disadvantage in terms of investigation[43]. If keloids or scars are large and multiple, initial therapy should include pressure therapy or therapy with a silicone gel

sheeting. Isolated lesions should be additionally treated with cryotherapy or 5-FU.

Big keloids need to be surgically treated in addition to some other methods. If the lesion is smaller, and if it is not located on the ear lobe, initial therapy should not be surgical but combined. Keloids of the ear lobe should be operatively treated, followed by some other therapy, e.g., pressure therapy, corticosteroids, 5-FU or laser therapy. Special care should be taken in the treatment of keloids and scars of the face in terms of concentration of corticosteroids and use of laser. Scars that are formed after acne can be treated by dermoabrasion[44].

Combinations of therapeutic methods and their precise use are the most important factors for successful treatment outcome.

References

1. DANG C, TING K, SOO C, LONGAKER MT, LORENZ PH. Fetal wound healing, current perspectives. Clin Plastic Surg 2003;30:13-23.
2. URIOSTE SS, ARNDT KA, DOVER JS. Keloid and hypertrophic scars: review and treatment strategies. J Cutan Med Surg 1999;2:159-71.
3. BAYAT A, Mc GROUTHER DA, FERGUSON MWJ. Skin scarring. BMJ 2003;326:88-92.
4. FERGUSON H. Body piercing. BMJ 1999;319:1627.
5. HENDRICKS WM. Complications of ear piercing: treatment and prevention. Cutis 1991;48:394.
6. DATUBO-BROWN DD. Keloids: a review of the literature. Br J Plast Surg 1990;43:70-7.
7. COSMAN B, CRIKELAIR GF, JU DM. The surgical treatment of keloid. Plast Reconstr Surg 1961;27:335-58.
8. ALHADY SM, SIVANANTHARAJAH K. Keloids in various races: a review of 175 cases. Plast Reconstr Surg 1969;44:564.
9. MONACO J, LAWRENCE TW. Acute wound healing, an overview. Clin Plast Surg 2003;30:1-12.
10. RUMALLA VK, BORAH GL. Cytokines, growth factors, and plastic surgery. Plast Reconstr Surg 2001;108:719-33.
11. GORTI KG, KOCH JR. Modulation of wound healing and scar formation. Curr Opin Otolaryngol Head Neck Surg 2002;10:287-91.
12. NISHIKORI Y, KAKIZOE E, KOBAYASHI Y, SHIMOURA K, OKUNISHI H, DEKIO S. Skin mast cell promotion of matrix remodelling in burn wound healing in mice: relevance of chymase. Arch Dermatol Res 1998;290:553-613.
13. BEER TW, BALDWIN H, WEST L, GALLAGHER PJ, WRIGHT DH. Mast cells in pathological and surgical scars. Br J Ophthalmol 1998;82:691.
14. ARMSTRONG DG, JUDE EB. The role of matrix metalloproteinases in wound healing. J Am Pediatr Med Assoc 2002;92:12-8.
15. RAHBAN SR, GARNER LW. Fibroproliferative scars. Clin Plast Surg 2003;30:77-89.
16. MUSTOE TA, COOTER RD, GOLD MH, HOBBS R, RAMELET AA, SHAKESPEARE PG, STELLA M, TEOT L, WOOD FM, ZIEGLER UE. International clinical recommendations on scar management. Plast Reconstr Surg 2002;??:560-71.
17. KETCHUM LD, COHEN IK, MASTERS FW. Hypertrophic scars and keloids: a collective review. Plast Reconstr Surg 1974;53:140-54.
18. MUIR JFK. On the nature of keloid and hypertrophic scars. Br J Plast Surg 1990;43:61-9.
19. VISHNU KR, GREGORY LB. Cytokines, growth factors, and plastic surgery. Plast Reconstr Surg 2001;108:719-33.
20. HOM DB, TIBESAR R. Growth factor therapy to improve soft tissue healing. Fac Plast Surg 2002;1:41-52.
21. TEPPER OM, MEHRARA BJ. Gene therapy in plastic surgery. Plast Reconstr Surg 2002;109:716-34.
22. HUNT JA, MOISIDIS E, HAERTSCH P. Initial experience of Integra in the treatment of post burn anterior cervical neck contracture. Br J Plast Surg 2000;53:652-8.
23. LEE Y, MINN K, RONG MIN BAEK, HONG JJ. A new surgical treatment of keloid: keloid core excision. Ann Plast Surg 2001;46:135-40.
24. HOFFMAN S. Radiotherapy for keloids? Ann Plast Surg 1982;9:205.
25. DARZI MA, CHOWDRI SK, KAUL SK, KHAN M. Evaluation of various methods of treating keloids and hypertrophic scars: a 10-year follow up study. Br J Plast Surg 1992;45:374-9.
26. CLAVERE P, BEDANE C, BONNETBLANC J, BONNAFOUX-CLAVERE A, ROUSSEAU J. Postoperative interstitial radiotherapy of keloids by iridium 192: a retrospective study of 46 treated scars. Dermatology 1997;195:349-52.
27. CARR COLLINS JA. Pressure techniques for the prevention of hypertrophic scar. Clin Plast Surg 1992;19:733-43.
28. RODERICK BJ, JOYCE D, WASIL K, STEVENSON JH, MCNEE J, GROVES AR, THOMAS SS, HART NB, AUCLAIR P. Splints and scar management for acute and reconstructive burn care. Clin Plast Surg 2000;1:71-85.
29. CARNEY SA, CASON CG, GOWAN JP. Cica care gel sheeting in the management of hypertrophic scarring. Burns 1994;20:163-7.
30. KATZ BE. Silicone gel sheeting in scar therapy. Cutis 1995;56:65-7.
31. NORRISH TE. The effect of carbon dioxide laser surgery on the recurrence of keloids. Plast Reconstr Surg 1991;87:44-9.
32. ALSTER TS, KURBAN AK, GROVE GL, GROVE MJ, TAN OT. Alteration of argon laser induced scars by the pulsed dye laser. Ann Plast Surg 1994;32:186-90.
33. ALSTER TS, WILLIAMS CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pupped pulsed dye laser. Lancet 1995;345:1198.
34. GOLDMAN M, FITZPATRICK RE. Laser treatment of scars. Dermatol Surg 1995,21:685-7.
35. FITZPATRICK R. Intralesional 5-FU in the treatment of hypertrophic scars and keloids: clinical experience. Dermatol Surg 1999;25:224-32.

36. FRIEDMAN SJ, BUTLER DR, DITTELKOV MR. Perilesional linear atrophy and hypopigmentation after intralesional corticosteroid therapy. J Am Acad Dermatol 1988;19:537-41.
37. EHRENSTORM REIZ G, REIZ S, STOCKMAN O. Topical anaesthesia with EMLA, a new lidocaine-prilocaine cream and the cusum technique for detection of minimal application time. Acta Anesthesiol Scand 1983;27:510-2.
38. LAYTON AM, YIP J, CUNLIFFE WJ. A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids. Br J Dermatol 1994;130:498.
39. RUSCIANI L, ROSSE G, BONO R. Use of cryotherapy in the treatment of keloids. J Dermatol Surg Oncol 1993;19:529.
40. LARABEE WF, EAST CA, JAFFE HS. Intralesional interferon gamma treatment for keloids and hypertrophic scars. Arch Otolaryngol Head Neck Surg 1990;116:1159-62.
41. PITTET B, RUBBIA-BRANDT L, DESMOULIEVE A. Effect of gamma interferon on the clinical and biological evolution of hypertrophic scars and Dupuytren's disease: an open pilot study. Plast Reconstr Surg 1994;93:1224.
42. BERMAN B, KAUFMAN J. Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. J Am Acad Dermatol 2002;47:209-11.
43. HILLMER MP, MacLEOD SM. Experimental keloid scar models: a review of methodological issues. J Cutan Med Surg 2002;4:354-9.
44. HIRSCH RJ, LEWIS AB. Treatment of acne scarring. J Cutan Med Surg 2001;3:190-8.

Sažetak

STRATEGIJE U LIJEČENJU KELOIDA I HIPERTROFIČNIH OŽILJAKA

D. Shejbal, V. Bedekovic, M. Ivkic, L. Kalogjera, Z. Aleric i P. Drviš

Keloidi i hipertrofični ožiljci posljedica su prekomjernog odlaganja kolagena tijekom cijeljenja rane. S povećanim brojm operacija i ozljeda, pojavom tzv. *piercinga*, te višim estetskim kriterijima poraslo je zanimanje za njihovo liječenje. Nedostatak životinjskog modela za proučavanje keloida upućuje na nužnost iskustva iz kliničke prakse. Terapija treba biti kombinirana, a postojanje različitih opcija dokazuje kako još uvijek ne postoji idealan oblik liječenja. Raspravlja se o molekularnim, biokemijskim i kliničkim vidovima razvoja keloida i hipertrofičnih ožiljaka, kao i o njihovom liječenju.

Ključne riječi: *Hipertrofični ožiljak – terapija; Hipertroficni ožiljak – fiziopatologija; Keloid – terapija; Keloid – etiologija; Cijeljenje rane – fiziopatologija; Poslijeoperacijske komplikacije –*