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Wound Healing Update

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The management of acute and chronic wounds has drastically changed within the past 20 years. This update focuses on the most recent recommendations for acute wound care as well as new technologies that are available for chronic wounds.
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Acute Wound Healing

Topical Antibiotics

Superficial acute wounds from dermatologic procedures were traditionally treated with topical antibiotics[1,2] based on early studies reporting that prophylactic topical antibiotics resulted in decreased infection rates and improved healing.[3,4] Current practices also emphasize the importance of a moist wound environment in accelerating healing.[5] The fact that many antibiotic ointments create such an environment promotes their use. However, a 1996 randomized control trial evaluating 922 patients with 1249 wounds treated with either white petrolatum or bacitracin found that 1.5% of patients in the white petrolatum group developed infections compared with 0.09% in the bacitracin group ($P = 0.37$), and researchers concluded that topical antibiotics are unnecessary for uncomplicated skin wounds.[6] Similarly, Campbell et al reported that in 144 auricular Mohs micrographic surgery wounds, there was no difference in the incidence of suppurative chondritis in patients treated with topical gentamicin versus white petrolatum.[7] Furthermore, there was no difference in healing or infection of shave biopsy sites when comparing Aquaphor Healing Ointment (Beiersdorf, Inc, Wilton, CT) with Polysporin (Poly/Bac, Johnson & Johnson, New Brunswick, NJ).[8]

Frequent use of topical antibiotics can cause problems. First, the development of resistant organisms is increasing, and there are few new antibiotics to combat this problem.[1] Exposure to mupirocin is a risk factor for developing methicillin-resistant *Staphylococcus aureus* resistance to this antibiotic.[9] In 1 study of 4980 methicillin-resistant *Staphylococcus aureus* strains, high-level mupirocin resistance increased from 1.6% to 7.0% between 1995-1999 and 2000-2004.[10] Second, antibiotic ointment can cause allergic contact dermatitis. Smack et al reported that 4 of 444 patients treated postprocedurally with bacitracin developed allergic contact dermatitis versus no cases in 440 patients treated with white petrolatum.[6] The prevalence of allergic contact dermatitis to topical antimicrobials is unknown in the general population. However, the sensitivity to neomycin and bacitracin ranges from 7.2% to 13.1% and 1.5% to 9.1%, respectively, in patients presenting for patch testing.[11] Another rare allergic consequence of topical antibiotics, particularly bacitracin, is anaphylaxis.[12,13]

Cleansing Acute Wounds

In the past, management of acute cutaneous wounds has included cleansing with many agents, including hydrogen peroxide and povidone-iodine.[14] Both chemicals reduce migration and proliferation of fibroblasts in a dose-dependent manner, and their undiluted use is not recommended. Silver-containing antiseptics and chlorhexidine also reduce proliferation at high concentrations but may enhance epithelial growth at lower doses.[15]

A 2008 Cochrane Review concluded that cleansing acute wounds with potable tap water is more effective at reducing infection rate compared with cleansing with saline.[16] For heavily contaminated wounds, high-pressure irrigation should be performed using a 10- to 50-mL syringe and splatter shield.[17]

Acute Wound Closure

Closure methodologies for surgical or traumatic wounds include sutures, staples, adhesive tapes, and glues. The punch biopsy, a procedure carried out daily by most dermatologists, is most commonly closed primarily with simple sutures.

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Table 1 A Review of Useful Dressings

Dressing Types	Examples	Advantages	Disadvantages
Films	Bioclusive (Johnson & Johnson, New Brunswick, New Jersey) OpSite (Smith & Nephew, London, England) Polyskin II by Kendall (Covidien, Dublin, Ireland) Tegaderm (3M, St Paul, MN)	Adherent Transparent Bacterial barrier	Fluid collection Can be difficult to apply or strip away newly formed epithelium with removal
Hydrogels	Derma-Gel (Medline Industries, Inc, Mundelein, IL) 2nd Skin (Spenco Medical Corporation, Waco, Tex) Vigilon (Bard Medical Division, Covington, GA)	Comfortable Absorbent Desloughing agents	Nonadherent Maceration of skin around the wound Cost
Hydrocolloids	DuoDERM (Convatec, Skillman, NJ) Restore (Hollister wound Care LLC, Libertyville, IL) Comfeel (Coloplast, Minneapolis, MN)	Enhanced wound healing Easy to use Cost-effective Promote granulation tissue	Unpleasant odor Yellow-brown, gel-like fluid drainage Difficult to use in cavities Can stimulate excess granulation tissue
Alginates	Maxorb Extra (Medline Industries, Inc, Mundelein, IL) Nu-Derm (Johnson & Johnson, New Brunswick, New Jersey) Tegaderm alginate Silver (3M, St Paul, MN)	Absorbent Useful in sinuses Hemostatic properties	Large quantities of saline to remove fibers on wound Frequent dressing changes for moist wounds Not useful for dry wounds
Foam dressings	Allevyn (Smith & Nephew, London, England) Lyofoam (Molnlycke Health Care, USA, LLC, Norcross, GA)	Absorbent Moist healing environment Conforms to body contours	Can adhere to wounds if exudate dries
Laminates	Biobrane(Smith & Nephew, London, England)	Recommended for superficial wounds	

However, suturing is not always necessary from a cosmetic, patient satisfaction, and economic perspective. Christenson et al completed a prospective, randomized study in which 82 patients underwent two 4- or 8-mm punch biopsies on the upper outer arms, thighs, or upper back. One site was closed with 1 interrupted 4-0 nylon suture, and the opposite site was allowed to heal by secondary intention. Using a visual analog scale, 3 physicians were unable to detect a difference in wound healing between biopsy sites allowed to heal primarily versus those that healed by secondary intention. Patients preferred suturing of the 8-mm, but not 4-mm, biopsy sites. By choosing secondary healing, the cost of biopsy procedures is reduced by saving on the cost of supplies and professional costs for suture placement and removal.[18]

Other alternatives to sutures are tissue adhesives (TAs), such as butylcyanoacrylate and octylcyanoacrylate. Advantages of using TAs in the appropriate clinical setting include decreased risk of needlestick injuries and avoidance of suture removal. Two reviews comparing TAs with standard wound closure (sutures, staples, adhesive tapes) found that there was no significant difference in cosmesis when treating traumatic lacerations. However, there were decreased procedure times and pain scores and a small increase in dehiscence rate with the former.[19,20] Conversely, TAs may not be the best option for closure of surgical wounds.[21] A Cochrane Review of 14 randomized controlled trials involving 1152 patients found a significantly increased risk of dehiscence with the use of TAs compared with sutures.[21]

An important principle that contradicts early beliefs about wound healing is maintenance of a moist wound environment. Until the 1950s, a dry wound environment was thought to be necessary to prevent bacterial growth.[22] However, in 1962, Winter demonstrated that epidermal healing was improved in a moist wound environment in animal models.[23] Soon after, Hinman and Maibach confirmed that this was also true for human skin.[24] A moist environment is considered essential for proper healing and is thought to prevent cellular dehydration and to stimulate cell migration, collagen synthesis, and angiogenesis.[15] Table 1 lists manufactured dressings designed to create a moist environment for wound healing.

Chronic Wound Healing

Evaluation of Lower-Extremity Wounds

Venous ulcers are the most common type of leg ulcer, comprising 50%-70% of all cases,[25] with a prevalence between 1% and 1.5%.[26] In the United States, ulcers in more than 6 million patients lead to treatment costs of $2.5 billion and 2 million workdays lost annually.[27] The etiology for venous ulcers is ambulatory venous hypertension resulting from reflux, obstruction, or

insufficiency of the calf muscle pump. Hypertension affects the superficial and deep venous systems as well as perforating vessels connecting both systems. Classically, venous ulcers are located in the gaiter region, from midcalf to ankle. Surrounding skin changes may include varicosities, pitting edema, dermatitis, and hyperpigmentation secondary to hemosiderin deposition.[26] These characteristics alone are often not sufficient to diagnose a venous ulcer. Particularly, if distal pulses are absent, arterial disease must be ruled out, and an ankle-brachial index is recommended to ensure the safe use of compression.[26] Duplex ultrasonography is the test of choice in evaluating for venous disease because it maps the anatomy of superficial, perforating, and deep veins and assesses blood flow, reflux, and obstruction.[25] Patients with chronic venous disease exhibit venous reflux in superficial veins in 90% of cases, perforator involvement in 20% of cases, and deep venous involvement in 30% of cases.[28]

Postthrombotic syndrome is another cause of venous ulcer disease.[29] In selected populations, such as young patients for whom the presence of a venous ulcer seems unusual, the cause of thrombosis should be investigated and coagulation defects should be ruled out. In 2000, Gaber et al found that in 53 patients with postthrombotic leg ulcers, 36% had activated protein C resistance secondary to factor V Leiden mutation, compared with 5% of healthy controls.[30] Other hereditary risk factors include prothrombin gene mutation G20210A, antithrombin deficiency, protein C and protein S deficiencies, homocystinuria, hyperhomocysteinemia, and antiphospholipid antibody syndrome.[31]

Treatment for Venous Insufficiency

Standard of care for the treatment of venous insufficiency and ulcers is compression. It is thought that external compression combats the increased hydrostatic pressure associated with venous insufficiency.[32] Forms of compression include the Unna boot (a noncompliant plaster dressing), multilayer compression bandages, short-stretch bandages, compression hosiery, and intermittent pneumatic devices. A 2009 Cochrane Review analyzed 39 randomized control trials that evaluated the efficacy of compression bandages or hosiery for venous ulcer healing. There is good evidence that compression is important for treating venous ulcers, and specifically, multicomponent systems, especially those containing an elastic component, are more effective than single-component systems.[32] A 2011 Cochrane Review analyzed the use of intermittent pneumatic devices for venous ulcer healing and found that they increase healing when compared with no compression. It remains unclear whether adding this methodology to bandage treatment improves healing.[33]

In the effect of surgery and compression on healing and recurrence (ESCHAR) randomized controlled study, Gohel et al evaluated 500 patients with open or recently healed leg ulcers and superficial venous reflux. Patients were randomized to treatment with multilayer compression alone or compression plus superficial venous surgery. At 3 years, 89% of patients in the compression group and 93% of patients in the compression plus surgery group had ulcer resolution ($P = 0.73$). However, ulcer recurrence rates at 4 years were 56% for the compression group and 31% for the compression plus surgery group ($P < 0.01$).[34] Thus, when duplex ultrasonography reveals superficial reflux in venous ulcer patients, surgical intervention to prevent recurrence should be part of the treatment regimen. Types of surgical intervention include conventional high ligation and stripping, as well as less invasive procedures, including endovenous thermal ablation (via radio frequency or laser) or chemical ablation. Thermal ablation results in less short-term side effects, such as pain, but more long-term studies are necessary to determine whether endovenous ablation is superior to classic surgical intervention.[35]

An oral adjuvant for difficult-to-heal venous ulcers is the hemorheologic agent pentoxifylline, which affects microcirculatory blood flow and oxygenation of ischemic tissues.[36] A 2009 meta-analysis of 12 trials, which evaluated 864 participants in all, reported that pentoxifylline is more effective than placebo for complete venous ulcer healing or marked improvement (relative risk [RR]: 1.70). Notably, 72% of patients reported gastrointestinal side effects.[36] Pentoxifylline is a poor solitary treatment for venous ulcer disease, but it is a useful adjunct. The target dose used in most studies is 400 mg 3 times daily, although a study by Falanga et al administered 800 mg 3 times daily.[36]

Bioengineered Skin Substitutes

Lower-extremity wounds that are recalcitrant to classic therapies are a difficult therapeutic challenge. A recent advance is the development of bioengineered skin substitutes, which have been Food and Drug Administration (FDA) approved for the treatment of recalcitrant diabetic foot ulcers and venous leg ulcers.

The first bioengineered tissues consisted of autologous keratinocyte sheets cultivated from a skin biopsy from the affected patient and were initially used to treat burn wounds.[37] Disadvantages included a lag time of 3-4 weeks for graft growth, fragility of the keratinocyte sheet, short-term graft stability, contracture, and slow regeneration of a "neodermis." Allogeneic keratinocyte sheets were developed, but they were still delicate and lacked a dermal component.[38]

As technology advanced, skin replacements composed of only dermal components included Dermagraft (Advanced Biohealing, Inc, Westport, CT), which consists of neonatal fibroblasts, seeded onto a biodegradable mesh, secreting collagen, glycosaminoglycans, fibronectin, growth factors, and other extracellular matrix proteins.[38] This is FDA approved for diabetic foot ulcer treatment. A bilayered construct, Apligraf (Organogenesis, Canton, MA), was the first commercially available composite tissue analog and is composed of fibroblasts and keratinocytes generated from neonatal foreskin. It is FDA approved for venous leg ulcers of >4 weeks' duration and for diabetic foot ulcers. Off-label, but reported, uses include epidermolysis bullosa, pyoderma gangrenosum, burn wounds, pressure ulcers, and ulcerative sarcoidosis.[39]

The mechanism of action of bilayered substitutes is unclear. It is thought that they supply necessary growth factors in the appropriate concentration and sequence that are otherwise lacking in chronic wounds. Also, the metabolic activity of young cells may supply larger numbers of growth factors.[38]

In a clinical trial of 120 patients with venous ulcers present for >12 months, 47% of Apligraf patients versus 19% of control patients had complete wound closure after 5 graft applications.[40] In a study of 208 diabetic foot ulcer patients, 56% of the Apligraf treatment group achieved complete wound healing compared with 38% of the control group.[41]

Growth Factor Therapy

Both granulocyte-macrophage colony-stimulating factor and platelet-derived growth factor (PDGF) have been shown to improve wound healing.[42] Data are limited, but both injected and topical interventions are useful in certain cases. In 60 venous leg ulcer patients injected with granulocyte-macrophage colony-stimulating factor, up to 61% demonstrated wound healing at 13 weeks versus 19% in the placebo group.[43] Topical recombinant human PDGF-BB (becaplermin) has been FDA approved for treatment of diabetic foot ulcers.[44] In a 4-center, randomized study including 922 patients, diabetic foot wounds showed up to a 39% increase in complete wound healing when treated topically with becaplermin gel (100 μg/g) compared with placebo group.[45] It may also be effective for nondiabetic foot ulcer wounds, leading to closure of 64% of such wounds in a small series of 14 patients.[44]

Stem Cell Therapy

Adult stem cells are tissue-specific, self-renewing cells that can differentiate into many cell types associated with their organ of origin. Populations that are potentially useful in wound therapy include bone marrow, adipose, umbilical cord, and, possibly, epithelial stem cells, such as follicular bulge cells.[46]

Adipose-derived stem cells (ASCs) cultured from liposuctioned or excised fat are relatively well-studied as a treatment for chronic wounds. Nie et al used a wound-healing rat model to present gross and histologic evidence that ASCs accelerate wound closure in normal and diabetic rats. ASCs differentiate into both epithelial and endothelial cell types and secrete angiogenic cytokines, suggesting their importance for neovascularization.[47] Additionally, ASCs promote dermal fibroblast proliferation by cell-to-cell contact and paracrine activation.[48]

Bone marrow-derived stem cells have also been shown to improve chronic wound healing. Fathke et al demonstrated that these cells promote wound healing in mice by increasing the dermal fibroblast population and collagen production.[49] In humans, Badiavas and Falanga applied autologous bone marrow cells to chronic wounds that had not responded to conventional therapy, bioengineered skin application, or skin grafting. All 3 patients experienced wound closure.[50]

Luo et al[51] reported improved wound healing in mice when human cord blood-derived mesenchymal cells were applied to wounds. Immunohistochemistry showed that these cells differentiated into keratinocytes in wound tissue. Zebardast et al recently used fibrin to deliver human umbilical cord perivascular cells to bilateral full-thickness defects created in nude mice. Compared with those receiving fibrin only, wounds that received stem cells demonstrated reepithelialization more quickly and thicker, better organized dermal tissue.[52]

Gene Therapy

Stem cells are a form of gene therapy, but genes can also be transferred directly to the skin using topically applied or injected DNA in the form of nonviral and viral vectors.[46,53] Nonviral vectors include liposomal sprays[54] and biphasic vesicles.[55] Nonviral gene therapy is less costly and avoids infection risk but tends to be nonspecific with variable levels of gene expression.[46] Long-term gene expression requires the integration of a gene into a cell's genome and is better accomplished by viral vectors. Retro- and lentiviral vectors have been integrated into cultured cells, such as stem cells, which are then injected into tissue. Adeno-associated virus vectors have led to long-term expression of genes after direct subcutaneous injection and topical application.[53]

Gene therapy can be used to promote granulation, vascularization, and reepithelialization and improve scar quality.[46,53] In a mouse model for diabetic foot ulcers, adenoviral-mediated gene transfer of PDGF led to improved vessel density, formation of granulation tissue, and enhanced epithelial gap closure when compared with controls.[56] Similar findings were reported in humans in a phase 1/2 study involving 15 patients with diabetic foot ulcers.[57] Adenoviral-mediated transfer of PDGF may be applicable to venous ulcers. In a 2009 phase 1 trial, Margolis et al reported that periulcer injection of an adenoviral construct expressing PDGF-beta was safe and feasible, resulting in granulation tissue and wound healing. Injection appears to be more effective than topical therapy.[58]

Conclusions

The practice of wound care has evolved during the past half century. Potentially surprising recommendations reviewed in this article include avoidance of topical antibiotics and the fact that punch biopsy wounds heal equally well with or without epidermal sutures. Although many tenets of chronic wound management, such as the importance of compression for venous ulcers, remain the same, there are many exciting advances in treatment for chronic wounds. Skin substitutes are now clinically available, and stem cell and gene therapy represent promising avenues for further advancements in wound care.

References

1. Del Rosso JQ: Wound care in the dermatology office: Where are we in 2011? J Am Acad Dermatol 64 Suppl 3:S1-S7, 2011
2. Sheth VM, Weitzul S: Postoperative topical antimicrobial use. Dermatitis 19:181-189, 2008
3. Forbes GB: Staphylococcal infection of operation wounds with special reference to topical antibiotic prophylaxis. Lancet 2:505-509, 1961
4. Heisterkamp C III, Vernick J, Simmons RL, et al: Topical antibiotics in war wounds: A re-evaluation. Mil Med 134:13-18, 1969
5. Field FK, Kerstein MD: Overview of wound healing in a moist environment. Am J Surg 167 Suppl:2S-6S, 1994
6. Smack DP, Harrington AC, Dunn C, et al: Infection and allergy incidence in ambulatory surgery patients using white petrolatum vs bacitracin ointment. A randomized controlled trial. JAMA 276:972-977, 1996
7. Campbell RM, Perlis CS, Fisher E, et al: Gentamicin ointment versus petrolatum for management of auricular wounds. Dermatol Surg 31: 664-669, 2005

8. Draelos ZD, Rizer RL, Trookman NS: A comparison of postprocedural wound care treatments: Do antibiotic-based ointments improve outcomes? J Am Acad Dermatol 64 Suppl 3:S23-S29, 2011
9. Caffrey AR, Quilliam BJ, LaPlante KL: Risk factors associated with mupirocinresistance in methicillin-resistant *Staphylococcus aureus*. J Hosp Infect 76:206-210, 2010
10. Simor AE, Stuart TL, Louie L, et al: Mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* Strains in Canadian hospitals. Antimicrob Agents Chemother 51:3880-3886, 2007
11. Gehrig KA, Warshaw EM: Allergic contact dermatitis to topical antibiotics: Epidemiology, responsible allergens, and management. J Am Acad Dermatol 58:1-21, 2008
12. Vale MA, Connolly A, Epstein AM, et al: Bacitracin-induced anaphylaxis. Arch Dermatol 114:800, 1978
13. James WD: Use of antibiotic-containing ointment versus plain petrolatum during and after clean cutaneous surgery. J Am Acad Dermatol 55:915-916, 2006
14. Howell JM, Chisholm CD: Outpatient wound preparation and care: A national survey. Ann Emerg Med 21:976-981, 1992
15. Thomas GW, Rael LT, Bar-Or R, et al: Mechanisms of delayed wound healing by commonly used antiseptics. J Trauma 66:82-90, 2009
16. Fernandez R, Griffiths R: Water for wound cleansing. Cochrane Database Syst Rev 23:CD003861, 2008
17. Singer AJ, Dagum AB: Current management of acute cutaneous wounds. N Engl J Med 359:1037-1046, 2008
18. Christenson LJ, Phillips PK, Weaver AL, et al: Primary closure vs second-intention treatment of skin punch biopsy sites: A randomized trial. Arch Dermatol 141:1093-1099, 2005
19. Farion KJ, Osmond MH, Hartling L, et al: Tissue adhesives for traumatic lacerations: A systematic review of randomized controlled trials. Acad Emerg Med 10:110-118, 2003
20. Beam JW: Tissue adhesives for simple traumatic lacerations. J Athl Train 43:222-224, 2008
21. Coulthard P, Esposito M, Worthington HV, et al: Tissue adhesives for closure of surgical incisions. Cochrane Database Syst Rev 12: CD004287, 2010
22. Korting HC, Schöllmann C, White RJ: Management of minor acute cutaneous wounds: Importance of wound healing in a moist environment. J Eur Acad Dermatol Venereol 25:130-137, 2011
23. Winter GD: Formation of the scab and the rate of epithelialization of superficial wounds in the skin of the young domestic pig. Nature 4812: 293-294, 1962
24. Hinman CD, Maibach H: Effect of air exposure and occlusion on experimental human skin wounds. Nature 4904:377-378, 1963
25. Gillespie DL, Kistner B, Glass C, et al; Writing Group III of the Pacific Vascular Symposium 6: Venous ulcer diagnosis, treatment, and prevention of recurrences. J Vasc Surg 52 Suppl 5:8S-14S, 2010
26. Van Gent WB, Wilschut ED, Wittens C: Management of venous ulcer disease. BMJ 341:1092-1096, 2010
27. Phillips T, Stanton B, Provan A, et al: A study of the impact of leg ulcers on quality of life: Financial, social and psychologic implications. J Am Acad Dermatol 31:49-53, 1994
28. Labropoulos N, Leon LR: Duplex evaluation of venous insufficiency. Semin Vasc Surg 18:5-9, 2005
29. Kistner RL, Eklof B, Masuda EM: Diagnosis of chronic venous disease of the lower extremities: The "CEAP" classification. Mayo Clin Proc 71: 338-345, 1996
30. Gaber Y, Siemens HJ, Schmeller W: Resistance to activated protein C due to factor V Leiden mutation: High prevalence in patients with post-thrombotic leg ulcers. Br J Dermatol 144:546-548, 2001
31. Osinbowale O, Ali L, Chi YW: Venous thromboembolism: A clinical review. Postgrad Med 122:54-65, 2010
32. O'Meara S, Cullum NA, Nelson EA: Compression for venous ulcers. Cochrane Database Syst Rev 1:CD000265, 2009
33. Nelson EA, Mani R, Thomas K, et al: Intermittent pneumatic compression for treating venous leg ulcers. Cochrane Database Syst Rev 2:CD001899, 2011
34. Gohel MS, Barwell JR, Taylor M, et al: Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): Randomised controlled trial. BMJ 335:83, 2007
35. Stoughton J: Venous ablation therapy: Indications and outcomes. Prog Cardiovasc Dis 54:61-69, 2011
36. Jull A, Arroll B, Parag V, et al: Pentoxifylline for treating venous leg ulcers. Cochrane Database Syst Rev 18:CD001733, 2007
37. O'Connor NE, Mulliken JB, Banks-Schegel KO, et al: Grafting of burns with cultured epithelium prepared from autologous epidermal cells. Lancet 317:75-78, 1981
38. Shen JT, Falanga V: Innovative therapies in wound healing. J Cutan Med Surg 7:217-224, 2003
39. Zaulyanov L, Kirsner RS: A review of bi-layered living cell treatment (Apligraf) in the treatment of venous leg ulcers and diabetic foot ulcers. Clin Interv Aging 2:93-98, 2007
40. Falanga V, Sabolinski M: A bilayered living skin construct (Apligraf) accelerates complete closure of hard-to-heal venous ulcers. Wound Repair Regen 7:201-207, 1999
41. Veves A, Falanga V, Armstrong DG, et al: Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: A prospective randomized multicenter clinical trial. Diabetes Care 24:290-295, 2001
42. Farah RS, Davis MD: Venous leg ulcerations: A treatment update. Curr Treat Options Cardiovasc Med 12:101-116, 2010
43. Da Costa RM, Ribeiro Jesus FM, Aniceto C, et al: Randomized, double-blind, placebo-controlled, dose-ranging study of granulocyte-macrophage colony-stimulating factor in patients with chronic venous leg ulcers. Wound Repair Regen 7:17-25, 1999
44. Harrison-Balestra C, Eaglstein WH, Falabela AF, et al: Recombinant human platelet-derived growth factor for refractory nondiabetic ulcers: A retrospective series. Dermatol Surg 8:755-759, 2002
45. Smiell JM, Wieman TJ, Steed DL, et al: Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: A combined analysis of four randomized studies. Wound Repair Regen 7:335-346, 1999
46. Gauglitz GG, Jeschke MG: Combined Gene and stem cell therapy for cutaneous wound healing. Mol Pharm 3:1471-1479, 2011
47. Nie C, Yang D, Xu J, et al: Locally administered adipose-derived stem cells accelerate wound healing through differentiation and vasculogenesis. Cell Transplant 20:205-216, 2011
48. Kim WS, Park BS, Sung JH, et al: Wound healing effect of adipose-derived stem cells: A critical role of secretory factors on human dermal fibroblasts. J Dermatol Sci 48:15-24, 2007
49. Fathke C, Wilson L, Hutter J, et al: Contribution of bone marrow-derived cells to skin: Collagen deposition and wound repair. Stem Cells 22:812-822, 2004
50. Badiavas EV, Falanga V: Treatment of chronic wounds with bone marrow-derived cells. Arch Dermatol 139:510-516, 2003
51. Luo G, Cheng W, He W, et al: Promotion of cutaneous wound healing by local application of mesenchymal stem cells derived from human umbilical cord blood. Wound Repair Regen 18:506-513, 2010
52. Zebardast N, Lickorish D, Davies JE: Human umbilical cord perivascular cells (HUCPVC): A mesenchymal cell source for dermal wound healing. Organogenesis 6:197-203, 2010
53. Jensen TG: Cutaneous gene therapy. Ann Med 39:108-115, 2007
54. Meykedah N, Mirmohammadsadegh A, Wang Z, et al: Topical application of plasmid DNA to mouse and human skin. J Mol Med Berl, Germany 83:897-903, 2005
55. Foldvari M, Kumar P, King M, et al: Gene delivery into human skin in vitro using biphasic lipid vesicles. Curr Drug Deliv 3:89-93, 2006
56. Keswani SG, Katz AB, Lim FY, et al: Adenoviral mediated gene transfer of PDGF-B enhances wound healing in type I and type II diabetic wounds. Wound Repair Regen 12:497-504, 2004
57. Mulder G, Tallis AJ, Marshall VT, et al: Treatment of nonhealing diabetic foot ulcers with a platelet-derived growth factor gene-activated matrix (GAM501): Results of a phase 1/2 trial. Wound Repair Regen 17:772-229, 2009
58. Margolis DJ, Morris LM, Papadopoulos M, et al: Phase I study of H5.020CMV.PDGF-beta to treat venous leg ulcer disease. Mol Ther 17:1822-1829, 2009