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A Concise Review on Scarless Wound Healing

Aswany U R*, Anzal N

Ezhuthachan College of Pharmaceutical Sciences
Marayamuttom, Neyyattinkara,
Thiruvananthapuram-695124

Abstract:

This review is focused on the scarless wound healing by using wound healing products, which typically aim either to reduce scarring , decrease the time of wound healing or to reduce inflammation.This review highlights basics of wound healing, strategies to reduce scarring ,role of silver nanoparticles in wound healing, the application of regenerative medicine in scarless wound healing. Pharmaceutical products including both traditional plant-based materials and proteins have been found as effective wound cures to reduce or eliminate scars.

Keywords: Epithelialization, Fibroblasts, Scar, Wound healing

INTRODUCTION

In adult (postnatal) mammalian organisms, injury to cutaneous tissue with disruption of normal skin architecture is repaired by means of an inflammatory and fibrotic response that leads to accumulation of scar. Although scar formation allows for the rapid sealing of an injured area, it can frequently prove the source of persistent pathology in the organism. Scar tissue forms in injured areas can replaces cells that have been destroyed. It appears either inside the body or on the skin. Scar tissue on the skin looks different from the surrounding area; while inside the body, scar may cause adhesion between tissues and organs or fibrosis. Scar causes functional impairment and emotional distress, thus the pre- or post-scar managements are important.

A scar is caused by the overgrowth of a tissue after an injury, burn, or surgical incision, demonstrating an exuberant healing response which determines type of scars: hypertrophic and keloid. Hypertrophic scars do not extend beyond the wound borders while keloid scars do. Hypertrophic scars are more manageable in treatment and are often more spontaneous in regression. In a keloid scar, thicker and more irregularly arranged collagen often with pain is observed. For a hypertrophic scar, however, patients encounter thinner and more parallel arranged collagen in scars. Moreover, hypertrophic scars arise in all races with low probability in young and aged people. Keloid scars, occur in non-white persons. Cutaneous scars have attracted more research work than the others from the cosmetic perspective.[1]

Wound healing process of a human adult can be classified into three distinct phases: (1) inflammatory, in which damaged and dead cells, along with pathogens or debris, are cleared out via the phagocytosis. Platelet-derived growth factors are released that cause the cells migration and division during the proliferation; (2) proliferation or new tissue formation and angiogenesis, collagen regeneration, growth of granulated tissue, epithelialization, and wound contraction occur; (3) remodeling stage, in which collagen is orientated along tension lines, and non-viable cells are removed by apoptosis. A number of growth factors and cytokines have been reported to be involved in the wound healing procedure through different biochemical pathways.

Scar formation is a prevalent, undesirable consequence of most wound healing events, along with significant psychological, emotional, and social problems. It is always desirable but difficult to develop wound treatment that allows prompt healing and less scarring, particularly in adult tissues. Accordingly, there have been considerable research and development efforts to not only accelerate the healing process but also prevent the scar or minimize the scar size in skin or other tissues. In addition, many different techniques to treat scars have been developed, including laser therapy, diverse types of sutures, and radiation therapy. Barbed sutures were evaluated clinically and were shown to provide comparable performance and safety as compared to conventional wound closure techniques. Applying of pulsed-dye laser with the immune response modifier (IRM) imiquimod as a topical agent on surgery scar areas may help reduce scar size.[2]

BASIC WOUND HEALING

The process of wound healing involves fundamental and coordinated interactions between damaged tissue, recruited inflammatory cells, and local fibroblasts. Wound healing involves a complex series of interactions between different cell types, cytokine mediators, and the extracellular matrix. The phases of normal wound healing include hemostasis, inflammation, proliferation, and remodeling.

Hemostasis

Initial injury leads to disruption of the vascular endothelium and exposure of the basal lamina, which result in extravasation of blood constituents and concurrent platelet activation which in turn is associated with clotting, aggregation and activation of these products and also result in the subsequent release of growth factors involved in the deposition of extracellular matrix (transforming growth factor β), chemotaxis (platelet-derived growth factor), epithelialization (fibroblast growth factor and epidermal growth factor), and angiogenesis (vascular endothelial growth factor).

Inflammation

Platelet activation is followed by an influx of inflammatory cells within the first 1 to 2 days, led by polymorphonuclear leukocytes. Neutrophils, monocytes,

fibroblasts, and endothelial cells deposit on a fibrin scaffold formed by platelet activation. Neutrophils is followed by monocytes, which are quickly activated into tissue macrophages. These cells are responsible for further tissue debridement and secrete additional cytokines and growth factors that promote fibroblast proliferation, angiogenesis, and keratinocyte migration. Their presence is considered vital for wound healing. They may also play a role in the apoptosis of neutrophils, thereby clearing cells that may otherwise result in a prolonged inflammatory stage.

Proliferation

Proliferation involves epithelialization, angiogenesis, granulation tissue formation, and collagen deposition. Epithelialization is initiated by keratinocytes present on the wound edge as well as from dermal appendages, such as hair follicles, sweat, and sebaceous glands. This begins with cell detachment and mitotic division and is stimulated by epidermal growth factor, fibroblast growth factor, transforming growth factor β, and multiple cytokines. Platelet-derived growth factor, fibroblast growth factor and vascular endothelial growth factor initiate and promote angiogenesis, which is of crucial importance for a healing wound. Angiogenesis involves the formation of thin-walled endothelium from pre-existing vessels. Fibroblasts first appear in the wound after 24 hours and require adequate oxygen supply for collagen production. Fibroblasts are also responsible for elastin production and organization of the extracellular matrix.

Maturation and remodeling

Wound maturation and remodeling result in a quickly healed and minimally visible scar, whereas prolongation or deviations from this phase can cause hypertrophic or keloid scars or chronic, nonhealing wounds. Wound maturation requires the reorganization of newly deposited collagen. Initially, fibroblasts multiply and increase collagen production per cell. An overall increase in collagen formation is seen for 4 to 5 weeks after wounding. A specialized version of the fibroblast, myofibroblasts are thought to lead to wound contraction. These cells express alpha-smooth muscle actin, which enables the cells to contract. They are also thought to contribute to angiogenesis during wound healing by decreasing matrix metalloproteinase activity.

STRATEGIES TO REDUCE SCARRING

Scars resulting from surgical incisions or cutaneous injury initiate a complex cascade of molecular and cellular events within a dynamic extracellular matrix. Treatment modalities capable of broadly influencing biological repair pathways hold the greatest potential for scar reduction. Strategies to minimize the appearance of these scars and restore the integrity of normal skin will be as follows:

Topical therapy & intraregional injections of corticosteroids:

Topical therapy and intraregional injections of corticosteroids is found to be the nonsurgical therapy for the treatment of keloids and hypertrophic scars. Steroids exert their effects by inhibiting the inflammatory response, suppressing fibroblast growth and promoting collagen degradation.

Triamcinolone, the most widely used agent, is able to inhibit TGF-β1 expression and induce apoptosis in fibroblasts, and inhibit TGF-β1, COL4A1, and COL7A1 in keratinocytes. Verapamil also reduce the production of interleukin-6 and vascular endothelial growth factor in fibroblasts harvested from the central portions of keloid scars. Topical agents based on plant extracts also exist. Mederma is a topical gel used to improve scar appearance, with the extract from the common onion as the main active ingredient. Onion extract contains a bioflavonoid with both antihistamine and antiproliferative effects. Mederma improves collagen organization.

The major drawbacks of this strategy is found to be hypopigmenta tion, dermal atropy, telangiectasia, delayed wound healing e.t.c. Success of this strategy in animals is not recapitulated in human clinical trial

Gene targets

A number of genes involved in the scarring response have been identified, which typically influences fibrosis by regulating collagen production and degradation. TGF-β is a major regulator of fibroblast physiology.TGF-β expression has been strongly implicated in the fibroblast-to-myofibroblast transition and in the production and secretion of extracellular matrix. The gene is expressed as three isoforms in humans with differential activity. TGF-β1 and TGF-β2 both promote fibrosis, whereas TGF-β3 has been shown to decrease fibrosis and scarring.

Therapeutic strategies targeting TGF-β signaling involve the use of either TGF-β1 and TGF-β2 inhibitors and neutralizing antibodies or up-regulating TGF-β3 signaling. Neutralizing antibodies bind directly to TGF-β1 and TGF-β2, preventing them from binding to and activating TGF-β receptors. These antibodies have successfully reduced fibrosis across a number of organs, including a reduction in cutaneous scarring following injury. Up-regulating TGF-β3 has also demonstrated efficacy in animal models, reducing scarring in a number of studies.

Dermal substitutes

Dermal substitutes provide coverage to the wound site and establish a matrix that encourages engraftment and proliferation of endogenous cells and enhances the function of transplanted cells.

Cellular matrices, derived from animal or human tissue through the removal of living cells, are biocompatible, remain morphologically similar to natural tissue structure, and have mechanical properties similar to host skin. Cellular matrices derived from human dermis currently in clinical use include AlloDerm, Derma Matrix, and FlexHD. Dermal substitutes using human chorion and amnion have also been used.

Epifix is composed of dehydrated human amnion/chorion membrane. Grafix is cryopreserved placental membrane with native mesenchymal stem cells used as

a covering to promote healing and tissue repair. Xenografts are skin substitutes for use in humans harvested from animals. The OASIS Wound Matrix, derived from the submucosal layers of porcine jejunum, is one of the more commonly used non–human-derived

acellular matrices in clinical use. Similarly, Surgisis is a biological graft extracted from porcine small intestinal submucosa. More recently, fetal bovine dermal matrices have becomes available, including PriMatrix and SurgiMend. Synthetic fabricated scaffolds are typically composed of proteins normally present in extracellular matrix. Matrices seeded with cells may also play a role in preventing scar formation.

Although dermal substitutes have not been shown to significantly impact scarring. The seeding of purified stem cell populations and niche components onto dermal substitutes may allow for a more significant role in scarring.

Mechanical offloading

An alternative approach to limiting fibrosis & reducing scar in the cutaneous injury is mechanical offloading. Mechanical tension plays a significant role in the development of fibrosis, activating a number of mechanoresponsive signaling pathways, with focal adhesion kinase. Langer lines in human skin corresponds to the natural orientation of collagen fibers within the dermis. Incisions made parallel to Langer lines generally heal with fewer scars (because of reduced tension). Paper tape and silicone sheets have been reported to reduce scarring. Application of paper tapes to closed surgical wounds for up to 12 weeks postoperatively reduce scar size and decrease the likelihood of developing a hypertrophic scar. To further improve the action of tapes, hybrid materials such as Dynaclose , a tape with a central region of silicone elastomer, have been developed.

Silicone gel sheets have been widely used since these sheets reduce tension on the wound site. These sheets have been proposed because of its scar-reducing effects such as hydration of the stratum corneum, direct modification of extracellular matrix composition, and decreased TGF-β2 expression in scar fibroblasts. Silicone gel sheeting placed over evolving hypertrophic and keloid scars led to reductions in scar size.

BIOMATERIALS FOR SCAR MANAGEMENT IN WOUND HEALING

Pharmaceutical products including both traditional plant-based materials and

Proteins have been found to be effective in wound healing to reduce or eliminate scars. These products should have to be used in combination with dressing or scaffolding biomaterials in wound care.

PHARMACEUTICAL PRODUCTS FOR SCAR MANAGEMENT

Pycnogenol: an extract from French maritime pine bark containing a mixture of procyanidins, was reported as a wound healing accelerator and scar formation reducer. Pycnogenol was suspended in a polyacrylic acid hydrogel and tested in vivo. Pycnogenol was found to decrease oxidized ascorbate and, consequently, to provide inhibitory effect on matrix metalloproteinases and to support collagen matrix formation.

Relaxin: Wounds treated with relaxin have less granulation and inflammation, and more well-knit collagen framework, representing that relaxin boosts the normal wound repair procedure by increasing angiogenesis, reducing scar formation and granulation tissue, and contributing to a well-organized collagen structure.

Astragalus membranaceus(AR): AR incorporated in a hydrophilic foam dressing is effective in increasing the closure of rats' acute open wounds. AR was found to suppress inflammation and promote basal cell proliferation, angiogenesis, and linear alignment of the granulation tissue and, consequently, to result in faster wound healing procedure.

Astragaloside IV: The healing and anti-scar effects of astragaloside IV on the wound cure improvement in vitro and in vivo. Astragaloside IV can inhibit the transforming growth factor beta 1 (TGF-β1) secretion and improve healing.It can regulate collagen type I/type III ratio in the remodeling phase to reduce scarring.

Crocodile oil: Enhance wound healing process and decreasing scar formation . Crocodile oil significantly decrease the messenger ribonucleic acid (mRNA) expressions of TGF-β1and Smad3, which are the key cytokines that play a role in accelerated wound healing and less scar formation

Curcumin: Curcumin improves lesion repair and reduces scarring. Curcumin was found to suppress TGF-β1/SMAD pathway and extra cellular matrix (ECM) production in primary keloid fibroblasts and reduce pro-inflammatory cytokines, interleukins (IL-1β, IL-6, and IL-8), which directly decrease hypertrophic scarring.

Honey: a traditional medical ingredient known for thousands of years, was reviewed for its healing and anti-microbial capacities. Honey stimulates monocytes (MM6 cells) to secrete cytokines, tumor necrosis factor alpha (TNF-α) and IL-1 and IL-6, which triggers the immune reaction to infection. Honey helps collagen IV degradation via the matrix metalloproteinases 9 (MMP9) stimulation during the reepithelialization phase of wound healing.

c-Ski: c-Ski is a tissue repair related gene that is mostly expressed in fibroblasts during the cell proliferation stage of wound healing. c-ski is capable of controlling scarring in wound repair by modulating fibroblast functions. c-Ski reduce scar by suppressing the production of protein in cutaneous wounds, as well as the effect of c-Ski in reducing scar size in a hypertrophic scar. It effects TGF-β1 signaling via Smad2/3-dependent and Smad-independent pathways that minimize scar formation and speed up wound healing.

Jun amino-terminal kinases (JNK): Jun amino-terminal kinases (JNK) signaling to mediate healing of corneal wound via expression of connective tissue growth factor, thus demonstrated that JNK can potentially serve as a new strategy to help in corneal scar reduction.

Calpains: calpains play a major role in granulation tissue formation. An inhibition of calpains, therefore, should be considered for treatments aiming at scar reduction.

Biomaterials composed of natural polymers

A number of biopolymers derived from natural resources have been used in wound care for reducing scar formation.

Hyaluronic acid (HA): fetal tissue heals rapidly without scarring due to the higher levels of hyaluronic acid (HA) in ECM as compared to adult tissues. Therefore, they observed that HA strand grafts enhanced wound closure rate and reduced the scar area remarkably by reducing TGF-β1 level in the wound. Injectable HA hydrogels were also used to improve wound healing and reduce scarring, resulting in remarkably less fibrosis than wounds. HA was found to maximize healing and minimize scar formation through preserving optimal viscoelastic properties of the ECM.The prophylactic use of a chemically modified HA hydrogel may increase the wound cure feature of HA in regenerating tissues by decreasing levels of fibronectin, fibromodulin, TGF-β1, procollagen I, and HA synthase and improving wound viscoelastic properties.

Genipin cross-linked gelatin (GCG) and collagen sheets: Genipin cross-linked gelatin (GCG) and collagen sheets were analyzed on minimizing invasion and scarring of the nerve and open wound healing in vivo. It was reported that GCG can be a beneficial aid for scarless nerve regeneration and lead to desirable nerve functional recovery.

Microbial cellulose: microbial cellulose have its effect on patients with second-degree facial burn. Compared to a standard technique with moist gauze dressing and ointment, the dressing considerably promoted the healing rate in deep facial burns. A decrease of pain and reduction of scar tissue formation were also observed for wounds treated by the microbial cellulose dressing. The moist environment created using the dressing facilitates necrotic debris removal, new cell migration and growth, and prompted reepithelialization.

Collagen membrane cross-linked with glutaraldehyde: Genipin cross-linked gelatin (GCG) and collagen sheets were analyzed on minimizing invasion and scarring of the nerve and open wound healing in vivo. It was reported that GCG can be a beneficial aid for scarless nerve regeneration and lead to desirable nerve functional recovery.

Electrospun nanofibrous dressings composited of silk fibroin/gelatin and cellulose acetate: Electrospun nanofibrous dressings composited of silk fibroin/gelatin and cellulose acetate have been examined in vivo and in vitro to prove their functionality in mimicking skin regeneration and in reducing scar formation. Wounds covered with the nanofibrous dressings showed increased expression of VEGF and existence of collagen type I which is similar to the normal skin. Electrospun silk fibroin nanomatrix fabricated as wound dressing materials were recently evaluated for burn wound repair as compared to clinically used dressings. Such an electrospun nanomatrix was found to reduce the wound healing period and scar formation. Amount of some involved growth factor and cytokines such as TGF-β1, IL-1α, 6, and 10 evaluated and ascertained their regulation that recovers epidermis.

CELL THERAPY AND TISSUE ENGINEERING SUBSTITUTE FOR SCAR MANAGEMENT

Cell therapy combined with scaffolding biomaterials have been employed in tissue engineering approaches for wound care and scar management.

Apligraf, a bi-layered bioengineered skin substitute, approved by the US Food and Drug Administration (FDA) is used for treating venous leg ulcers and diabetic foot ulcers.

The graft is developed from neonatal cells and may stimulate a more fetal-like scarless wound healing, therefore may result in better cosmetic appearance. Dermal and epidermal substitutes have been developed to help facilitate reepithelialization. Cellular therapies can be delivered by 3-dimensional structures (tissue-engineered live cell structures) that can be put topically over wound and scar surfaces as creams or gels.

Fetal cells are differentiable cells with high capacity of expansion, regeneration, and low immunogenic properties and therefore may induce scarless wound healing or minimal scarring. Skin substitutes developed from neonatal or young foreskin tissue cultures were shown to close wounds completely and rapidly and to regenerate the tissues with minimal scarring. They promote epithelial cells and fibroblasts proliferation and migration changes.

The mast cells may regulate the changes from scarless to fibrotic healing. Therefore in the absence of mast cells, scar formation can be controlled and reduced.

The mesenchymal stem cells (MSCs) attenuate scar formation during wound healing by promoting angiogenesis and modulating the inflammatory responses. MSCs can simulate endogenous cardiac stem cells to proliferate and differentiate, and adult cardiomyocytes re-enter the cell cycle via secreting plenty of growth factors and cytokines. Beside, artificial dermis consisted of type I collagen fiber coated with 3% a-elastin hydrolysate reduced human burn wound contracture and promoted dermal reconstruction. Recently MSCs were encapsulated in and delivered by gelatin microsphere and gelatin microcryogels to the margins of dermal wound and were found to accelerate wound closure rate and prevent scarring by maintaining MSC-released protein.

The 3-dimentional graphene foam (3D-GF) loaded with MSCs decreases scar formation, potentially because of biomechanical and biochemical signals from 3D-GFs. The foam provided up regulation of VEGF (Vascular endothelial growth factor) and bFGF to neovascularize, down regulation of Transforming growth factor TGF-β1 and alpha-smooth muscle actin (α-SMA) together with an enhancing of TGF-β3 to prevent scarring.

Polyhydroxybutyrate-co-hydroxyvalerate constructs loaded with adipose-derived stem cells (ASCs) were shown to maintain the wound moisture and assert appropriate mechanical properties to endure wound contraction. Furthermore, exudate and inflammatory cell infiltration were found to promote the structure degradation and, consequently, improve scarless repair.

ROLE OF SILVER NANOPARTICLES IN WOUND HEALING

Wound healing proceeds through an overlapping pattern of events including coagulation, inflammation, proliferation, and matrix and tissue remodeling. For this efficient and highly controlled repair process to take place, numerous cell-signaling events are required. Although cytokines are crucial in initiating, sustaining, and regulating the post-injury response, these same molecules have been implicated in impaired wound healing, abnormal scar formation, and uncontrolled inflammatory response.

For many years, silver sulfadiazine has been the standard treatment for burns, but some of the benefits of pure silver appear to be lost. Recent advances in nanotechnology have resulted in the ability to produce pure silver as nanoparticles. The wound-healing properties of silver nanoparticles shown rapid healing and improved cosmetic appearance occur in a dose-dependent manner. The quantitative PCR, immunohistochemistry, and proteomic studies showed that silver nanoparticles exert positive effects through their antimicrobial properties, reduction in wound inflammation, and modulation of fibrogenic cytokines. These results have given insight into the actions of silver and have provided a novel therapeutic direction for wound treatment in clinical practice.

Silver nanoparticles mainly work on the burns than that of other wounds. Silver nanoparticles exhibit cytoprotective activities toward infected cells. Silver nanoparticles can promote wound healing and reduce scar appearance in a dose-dependent manner. The silver nanoparticles act by decreasing inflammation through cytokine modulation. The potential benefits of silver nanoparticles in all wounds can therefore be enormous.

Silver nanoparticles promote healing and achieve better cosmesis

The wounds treated with silver nano particles shown the most resemblance to normal skin, with less hypertrophic scarring and nearly normal hair growth on the wound surface. Silver nanoparticles accelerate wound healing and achieve superior cosmetic outcome.

Silver nanoparticles have effective antibacterial properties

silver is known to be an effective antibacterial agent. Wound culture showed no microorganism growth up to 7 days after injury treated with silver nano particles. This confirmed that silver nanoparticles are a more effective antibacterial agent. With this in mind, we then compared silver nano particles with amoxicillin and metronidazole, two commonly used antibiotics. Wounds treated with silver nano particles completely healed in less days after injury than that of the antibiotics.

Silver nanoparticles play a role in cytokine modulation

cytokines play an important role in wound healing. evels of IL-6 mRNA in the wound areas treated with silver nanoparticles were maintained at statistically significant lower levels throughout the healing process. mRNA levels of TGF-b1 were higher in the initial period of healing. IL-10, VEGF, and IFN-g, mRNA levels stayed higher on time of healing. The differences found in mRNA levels of various cytokines confirm that silver can modulate cytokine expression.

SCARLESS HEALING THROUGH THE APPLICATION OF REGENERATIVE MEDICINE

When insult to the skin occurs, the body must undergo wound healing in order to restore the cutaneous barrier and prevent infection. However, the process of wound healing leads to incomplete regeneration of the original tissue, which results in a new layer that is less tensile, has lost its dermal appendages such as hair follicles and sebaceous glands, and frequently leads to pathological scarring which can cause pain, itching, cosmetically unappealing appearance, and decreased function and mobility.

A number of interventions have been attempted throughout history to facilitate wound healing and skin repair, yet despite these treatments, the healthcare costs and quality of life implications that arise from non-healing wounds, scarring, and skin aging continue to challenge individual patients as well as the healthcare economy.

This chapter describes novel and emerging scientific breakthroughs and technologies to promote healthy wound healing and skin repair using regenerative medicine, the future of scarless wound healing.

CURRENT UNDERSTANDING OF NATURAL WOUND HEALING AND AGING PROCESSES

Natural wound healing in response to insult or injury occurs in 3 major phases involving inflammation, proliferation, and maturation (remodeling). Each of these processes is regulated by numerous cytokines that suppress or promote different functions to maintain homeostasis during wound healing, and imbalances may lead to abnormal wound healing, such as chronic wounds or hypertrophic scar formation.

In addition to injuries or burns, the skin is also subject to aging, a physiologic process comprised of intrinsically genetically predetermined factors and extrinsic environmental and lifestyle factors.

Characteristics of skin aging included the development of fine wrinkles, skin thinning, and increased laxity of the skin which can caused by intrinsic and extrinsic factors. Intrinsic skin aging is caused by accumulated damage to DNA due to oxidative damage that occurs through cellular metabolism. Extrinsic aging is can be caused by UV light, pollution, smoking, alcohol and diet and can lead to DNA mutations and protein aging modifications that lead to increased degradation of collagen, abnormal elastin, and loss of glycosaminoglycans (GAGs), which are responsible for the integrity and hydration of the skin.

NON-REGENERATIVE PARADIGM FOR ACCELERATING WOUND HEALING

A number of non-regenerative techniques are currently being implemented to accelerate wound healing and promote skin vitality. Debridement plays an important role in wound healing to prevent devitalized, necrotic tissue

from increasing risk of infection and/or interfering with re-epithelization and contraction.

Treatment methods such as hyperbaric oxygen and local oxygen therapy are currently used for recalcitrant wounds based on the understanding that improved wound oxygenation is important for cell proliferation, immune response, angiogenesis, collagen synthesis, and epithelialization.

Other therapies to treat burns, wounds, and skin aging include operative techniques such as scar revision surgeries (z-plasties), tissue transfers and grafts, and non-operative techniques such as injections and ablative and non-ablative procedures. Flaps, grafts, and surgical revisions of burns or scars can help to camouflage scars but can never truly erase them.

Skin injections used to treat scarring include steroid injections to flatten scars and reduce symptoms, and collagen and fat filler injections for depressed scars. The disadvantage of injections is the potential for contour irregularities, and results may be influenced by the skill of the provider.

THE FUTURE OF SCARLESS WOUND HEALING

Ideal wound healing should achieve complete restoration of the skin structure and functions with minimal to no scarring over a short period of time with minimal discomfort to the patient. Regenerative healing uses cell-based therapies to promote scarless wound healing by replacing, engineering, or regenerating human cells, tissues, or organs.

Theoretically, the regenerative approach could revolutionize wound healing by providing an adequate microenvironment and carefully selected cells to replace missing components in injured tissue in order to modulate inflammation, release growth factors, and stimulate native cell populations to heal. One method that has been proposed to induce regeneration within the tissue is called percutaneous wound induction (PCI) and uses multiple needle application to treat scars and wrinkles.

PCI is a technique of rolling tiny needles in multiple directions to generate thousands of micro wounds in the dermis, thereby resulting in a natural, confluent, superficial post-traumatic dermal inflammation that employs the normal inflammatory wound cascade, without the risk of dyspigmentation. . Because PCI works by creating narrow clefts in the epidermis and stratum corneum, the epidermis is left intact with no dermabrasive reduction in epidermal thickness, and it minimizes exposures to stressors such as air, infection, and mechanical tension.

Other regenerative techniques involve correcting extrinsic defects that lead to abnormal skin healing, by delivering molecular therapies directly to the wound. For example, deferoxamine (DFO) is an iron chelator that increases HIF-1α activity by preventing ironinduced reactive oxygen species and subsequent oxidative stress. It can be delivered in a trans delivery system or “patch” to help prevent ulcerations and accelerate healing in chronic wounds. Novel drug delivery systems have been designed such as microspheres, nanoparticles, liposomes, sponges and wafer, and nano and microemulsions to provide controlled, targeted delivery of drugs to wounds while creating an optimum environment for healing.

Novel scaffolding to lay the selected cells onto can enhance growth factor production, increase survival of delivery cells, and promote scarless healing. One such scaffolding employs a biomimetic regenerative extracellular matrix component (pullulan-collagen) that is present during scarless embryonic healing to create a hydrogel dressing. This skeleton framework can then be layered to mimic the normal layers of the skin, so that each layer has cell properties and surrounding milieu that is unique to the stratification of normal skin.

CONCLUSION

Healing of wounds, whether from accidental injury or surgical intervention, involves the activity of an intricate network of blood cells, tissue types, cytokines, and growth factors. Adult (postnatal) skin wound healing is a complex and well-orchestrated process spurred by attendant inflammation that leads to wound closure with scar formation. Scars have the potential to exert a profound psychological and physical impact on the individual. Beyond aesthetic considerations and potential disfigurement, scarring can result in restriction of movement and reduced quality of life. The formation of a scar following skin injury is a consequence of wound healing occurring through reparative rather than regenerative mechanisms.

Topical therapy and intralesional injections of corticosteroids have formed the mainstay of nonsurgical therapy for the treatment of keloids and hypertrophic scar. Dermal substitutes encourages engraftment and proliferation of endogenous cells and enhances the function of transplanted cells. Paper tape and silicone sheets have been reported to reduce scarring. Matrices seeded with cells may also play a role in preventing scar formation.

Pharmaceutical products including both traditional plant-based materials and proteins have been found as effective wound cures to reduce or eliminate scars. It may include Pycnogenol, Relaxin, Astragalus membranaceus (AR), Honey etc. Cell therapy combined with scaffolding biomaterials have been employed in tissue engineering approaches for wound care and scar management. Silver nanoparticles has been found to be effective in rapid wound healing and improved cosmetic appearance which occurs in a dose dependent manner.

This review discussed several investigated ways and wound managements which are more likely to provide better cosmetic outcomes by scar reduction. Generally, understanding different types of treatments in human wound healing process in order to perfectly regenerate their missing cell and tissue and may propose strategies and methods for maximizing healing benefits and decreasing scarring.

BIBLIOGRAPHY

1. Rahimnejad M, Derakhshanfar S, Zhong W. Biomaterials and tissue engineering for scar management in wound care. Burns & trauma. 2017;5(4):2-9
2. Walmsley GG, Longaker MT. Scarless wound healing: chasing the holy grail. PRS journal**.** 2015;135(3):907-917
3. Moore AL, Marshall CD, Michael T Longaker. Minimizing skin scarring through biomaterial design. Journal of functional biomaterials. 2017;8(3):1-16
4. Satish L, Kathju S. Cellular andMolecular Characteristics of Scarless versus Fibrotic. Dermatology Research and Practice. 2010; 10(1155):1-9
5. Iqbal1 A, Jan A, MA Wajidh, Sheikh Tariq. Management of chronic non-healing wounds by hirudotherapy. World journal of pharmaceutical sciences. 2017;6(1):9-17
6. Hirsch RJ. Scarless Wound Healing. Marcel dekker. 2001;67:431
7. Janis JE, Harrison B. Wound healing:basic science. PRS journal. 2016;138(3S):9-17
8. Canesso MCC, Vieira AT, Tiago B R. Skin Wound Healing Is Accelerated and Scarless in the Absence of Commensal Microbiota. The journal of immunology. 2014;193: 5171–5180.
9. Roh TS, Rah DK, Park DY. The Fetal Wound Healing. *Yonsei medical journal. 2001;41(6):630-633*
10. MacKay D, Miller L. Nutritional support for wound healing, Alternative medicine review. 2003;8(4):359-377