

WOUND HEALING: A REVIEW

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ABSTRACT: Wound healing is one of the major problems faced by mankind. The healing of wound is a complex process that involves a series of reactions. In the developing countries like India and China traditional herbal drugs and their products are used for the treatment of wounds along with allopathic or the western system of medicine. This review comprises of the various aspects of wound and its healing, the herbal drugs that are used and also the modern technologies used in wound healing.

Key words: wound healing, allopathy, traditional drugs.

INTRODUCTION

Discontinuity or break in the surface of the epithelium is called wound. Wound and its management is one of the major problems in the world. The wounds can be caused due physical, chemical and biological agents. Wounds can be classified based on their etiology, lasting period, morphological characters etc. Later the color code concept was used wherein the wounds were classified as red yellow or black.

Based on the nature and depth wounds can be classified as:

Closed wounds: i.e. contusions, abrasions, and haematoma.

Open wounds: i.e. incised, lacerated, penetrating and crushed.

Depending on the intensity of the wound they can be termed as (a) Simple wound: Here the damage is only to the skin. (b) Complex wound: The wound involves the underlying tissues, tendons etc¹.

Wound healing is a complex process, which involves interactions among a variety of different cell types. Normally wound-healing process involves inflammation, proliferation and remodeling which occur in a series of cellular and biochemical events.

GENERAL PROCEDURE FOR WOUND REPAIR:

Wound healing is essentially a survival mechanism and represents an attempt to maintain the normal anatomical structure and function.

Wound repair involves two distinct processes i.e. (1) Regeneration of the injured tissues by paranchymal cell, which includes cell migration and cell multiplication.

(2) Wound contraction and Replacement of connective tissue.

The healing wound is a dynamic and changing process, which consists of inflammation (inflammatory phase 0-5 days) which starts at the moment of injury, this is followed by stage of fibroplasias (proliferative phase 3-14 days) which is followed by tissue remodeling (maturation phase day7-1year) and scar formation, which is the final product of healing process. Collagen is a major protein of the matrix and contributes to wound healing. Breakdown of collagen leads to liberation of free hydroxyproline.

Histamine, which is a mediator of inflammation, is released from the platelets and mast cells when injury occurs. This brings about an increase in capillary permeability. This is followed by the release of kinins and prostaglandin.

Different mechanisms occurring at different time triggers the realize of chemical signals that modulate the orderly migration, proliferation and differentiation of cells and the synthesis and degradation of ECM proteins. These proteins in turn directly affect cellular events and modulate cell response to soluble growth factors².

HEALING OF WOUND

Healing of wound can occur by (1) First or primary intention: This is seen when the wound is a clean incised wound. Healing proceeds rapidly with early closure of wound.

(2) Secondary intention: This is in the case where the wound edges are separate and there is tissue loss and sometimes the wound may be infected. Rapid closure of the wound is not possible therefore this leads to an ugly scar and sometimes may cause limitation of movement³.

FACTORS AFFECTING WOUND HEALING:

The factors affecting wound healing can be classified as:

(a) General (b) Specific (c) Drugs

General factors include local and systemic factors

Local factors

Blood supply: This is one of the basic factors in the success of wound repair.

Radiation: Radiation affects the wound especially on the skin wounds. It may have early or late effect on the skin and it is the late effect that is relevant to wound healing⁴

Infection: Any infection can cause a delay in healing of a wound.

Local wound environment: wounds that are moist or wet heal faster than the dry wounds⁵. Oxygen in chemically dissolved form in aqueous solution is reported to enhance wound healing⁶.

Systemic factors

Age: Investigations on experimental animals have revealed no evidence of impaired wound healing in older animals⁷.

Nutrition: It has prolonged effect on wound healing. Nutritional deficiencies can cause delay in wound healing and nutritional factors required for wound repair may improve healing time and wound outcome. It is therefore necessary and important to study the nutritional factors that promote wound healing with minimal time, pain, discomfort, and scarring⁸.

Vitamin deficiency: Vitamin C is required for collagenation and its deficiency causes impaired wound healing. Vitamin A is required for epithelial and bone formation^{7,9}.

Oxygen: is required for cell migration, cell multiplication and protein synthesis. Low oxygen has adverse effect on wound healing¹⁰.

Immuno suppression: wound healing is affected by immuno suppression by drugs or any other factors¹¹.

Trace elements: Trace elements like zinc and copper help in collagen synthesis .It is reported that zinc reverses the healing effect of cortico steroids¹² and non steroidal anti inflammatory agents¹³.

Specific factors:

Growth factors: These play an important role in cell division, migration, differentiation, protein expression, and enzyme production and have an ability to heal wounds by stimulating angiogenesis and cellular proliferation. Epidermal growth factor (EGF), cause epidermal proliferation and is also a mitogen for fibroblast. It has been reported that application of EGF can stimulate wound healing¹⁴. It was reported that the fibroblast growth factor was stimulated by soluble factors derived from macrophages in culture¹⁵. The other growth factors involved in wound healing are Platelet derived growth factor; Monocyte derived growth factor, and Transforming growth factor-B.

Hormones: Hormones are secreted during injury. Anabolic steroids like Nandrolone have been shown to have no effect on tensile strength when used alone but reverse tensile strength lowering effect of cortico steroids¹⁶.

Autacoids: Depletion of histamine retards wound healing, as it is one of the mediators of inflammation this results in lowering of tensile strength¹⁷, it was reported that formation of collagen is accelerated by histamine during wound healing¹⁸. The growth of fibroblasts is retarded in the presence of H₁ blockers, this in turn retards wound healing¹⁹.

The other factors that affect wound healing are metabolic status, circulatory status, mechanical factors like early moment of the wound presence of foreign bodies, diseased condition like diabetes, and size, type and location of wound etc.

Drugs

A number of drugs ranging from analgesics to chemotherapeutic agents, which have been used in the management of wounds act in different ways.

The wounds treated with Phenytoin showed significant increase in collagen deposition and neovascularisation, which resulted in an increase in wound tensile strength and improved healing of both open and closed wounds²⁰. Local application of Xylocaine in the form of jelly or ointment promoted re-epithelization²¹. Calcium channel blockers like Nifedipine can be used to enhance wound healing in steroid suppressed wound healing²². using a combination Bismuth subgallate (BS) and Borneol (BO) has best effect on healing by decreasing lesion area, while increasing granulation, tissue formation, and re-epithelization. The wound healing of this combination was attributed to the synergic effect on the wound²³. Vitamin E, Sodium pyruvate, and specific unsaturated fatty acids are reported to enhance healing of infected and non-infected wounds by reducing the damage caused by oxygen radicals²⁴.

Drugs like Aspirin¹³, Indomethacin²⁵, Tolmetin²⁶, Efenamic acid²⁷, Cytotoxic agents²⁸, Immunosuppressants²⁹ and radiations³⁰ have been proven experimentally to adversely affect wound healing which can be reversed by supplementations of vitamin E³¹ and growth factors like PDGF, EGF etc³². Generally all anti cancerous drugs adversely affect the wound healing process when used before surgery. Cyclophosphamide is known to interfere with epithelization, wound contraction, tensile strength and granulation formation³³.

Thus the management of wound healing is a complicated and expensive program

PATHOLOGIC ASPECTS OF WOUND HEALING

The process of wound healing can be complicated if any abnormalities occur during the repair process. These aberrations can be of three types:

Deficient scar formations: This can lead to wound dehiscence (i.e. rupture of wound due to pressure) and wound ulceration (due to inadequate vascularization during healing).

Excessive formations of the repair components: Excessive formation of collagen may give rise to raised tumourous scar called keloid or a hypertrophic scar. Similarly excessive amounts of granulation tissue protrudes above the level of normal skin, this is called exuberant granulation.

Formation of contractures: The size of the wound contracts in the normal healing process. If this does not happen it results in a contracture which causes deformities of the wound and the surrounding tissue.

Pigmentation of the skin: Improper healing may sometimes cause pigmentation of the skin¹.

TREATMENT OF WOUNDS

Wound healing is a global problem, more so in the developing world where only traditional medicine that are easily available, affordable, effective, and acceptable are more often used. A number of drugs are available to aid healing of wounds. They may act by increasing the growth factors, increase the blood flow and temperature, provide local energy sources, control infection or reduce edema. They can be selected depending on the condition of the wound and the phase of wound healing. In India and China the traditional system of medicine flourish in parallel with the Allopathic or western system of medicine

(1) WOUND CLOSURE:

Wound closure can be done by³:

Primary suturing: Here the wounds are sutured within a few hours after injury.

Wound excision and primary suturing of the skin: This is done when the wound edges and tissues are crushed, jagged, and infected. In this case the wound is washed with an antiseptic, cleaned and then sutured.

Wound excision and delayed primary suturing: This is usually in case of lacerated wounds with crush injuries. Here the suturing is not done immediately due to edema, contamination with bacteria etc.

Secondary suturing: Sometimes sutures may give away due to some pressure this may lead to secondary suturing.

(2) USE OF ANTIBIOTICS:

Infection is the major complication of the wound. The intact epithelial surfaces act as a barrier against infections under normal conditions, but in case of wounds there is a break down in these surfaces, thereby exposing the wound to the surrounding and making the wound susceptible to infections. The other mechanisms for protection against infection are (a) chemical: low gastric pH. (b) humoral (c) cellular: phagocytic cells, macrophages, killer lymphocytes etc.

The different types of wound infections are wound abscess, cellulites and lymphangitis, bacteraemia and septicemia and specific infections like gangrene.

The various bacteria that are involved in the wound infection are *Streptococcus faecalis*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Clostridium tetani*, *Clostridium perfringens*, *Escherichia coli*, *Klebsilla*, *Pseudomonas* etc.

A number of antibiotics have been used in the treatment of wound infections, which may be bacteriostatic or bactericidal³. Benzyl penicillin is most effective against gram-positive bacteria like *streptococci*, *clostridia* and some of the *staphylococci* that do not produce beta lactamase. Flucloxacillin and Methicillin are used in the treatment of staphylococcal beta lactamase resistant penicillin. Amphotericin and Amoxicillin can be given either orally or parenterally. They are active against enterobacteria but not *Klebsiella* or *pseudomonas*. Mezlocillin and Ozlocillin are ureido penicillins and are active against entero bacteria and *klebsiella*. Beta lactamase stable cephalosporins like Cefuroxime, Cefotaxime, Ceftazidime are used. Amino glycosides like Gentamycin and Tobramycin are effective against gram-negative enterobacteria. Imidazoles are effective against anaerobic bacteria and are considered safe. In case of wounds caused by bites a combination of extended spectrum of penicillin with a beta lactamase inhibitor is ideal. e.g. amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, ampicillin/sulbactam etc.

Silver sulphadiazine, Mafenide cream and Silver nitrate are the three widely used topical agents in case of burn wounds³⁴.

(3) HERBAL DRUGS:

A number of medicinal plants have been evaluated for wound healing activity with the intention of searching for agents with maximum activity and least toxicity. Approximately one third of the traditional medicines are for the treatment of wounds or skin disorders compared to only 1-3% modern drugs³⁵. Many plants and plant products that have been used and marketed as wound healing agents have been described below:

Aloe Vera (lilliaceae):

Proteins and saccharides present in the extract of *aloe vera* have been reported to aid the process of wound healing. It has also been shown to have anti-inflammatory effect on damaged skin and to enhance the healing of burn wounds^{36,37}. It is available in the form of creams and gels that are used to treat wounds, burn wounds and radiation wounds.

Calendula officinilis (Asteraceae):

This showed marked physiological regeneration and epithelization, which is attributed to the more intensive metabolism of the gluco, nucleo and collagen proteins during the regenerative period³⁸. *Calendula officinilis* is available in the form of healing creams (Weleda care products)³⁹.

Curcuma longa (zingiberaceae):

Curcumin isolated from *curcuma longa* when applied topically on the wound supports dermal healing. It causes increased wound reduction, cell proliferation and free radical scavenging⁴⁰. The volatile functions act as external antibiotics and prevent infection of the wounds.

Terminalia arjuna (combretaceae):

Terminalia arjuna is the active constituent of the commercially available Himax ointments, lotions and creams that are used for wound healing. It enhances the epithelization period and tensile strength and was comparable to standard nitrofurazone⁴¹.

Terminalia chebula (combretaceae):

Terminalia chebula is one of the ingredients in the commercially available Triphala along with *Terminalia bellerica* and amla. It is considered to be a strong healing agent when applied topically⁴².

(4) USE OF GROWTH FACTORS:

Growth factors are a large functional group of polypeptide regulating molecules secreted in different cells. They control the growth, differentiation and metabolism of cells, they provide a means by which the cells are able to communicate with each other, they regulate and influence the synthesis of the composition of extra cellular matrix components. They are mediators for the undisturbed repair process during wound healing. External application of the growth factors can modify the healing process. The use of specifically designed and modified growth factors; its inhibitors and proper dose regime offer further possibilities for increasing the healing of wound⁴³. The external application of growth factors have been reported to heal wounds, this is because the growth factors play an important role in wound healing. Different growth factors like TGF, PDGF, and PDAF etc; have been evaluated for wound healing activity and have been reported to increase the wound healing activity. Decrease in skin graft donor site healing by one day has been reported on topical application of EGF. It has also been reported that collagen deposition and keratinocyte migration was increased on topical application of thymic peptide thymocin beta 4⁴⁴.

(5) PLASTIC SURGERY OR RECONSTRUCTION:

This is a combination of surgical skills and techniques to modify a wound such that it heals faster. Plastic surgery involves making of a surgical wound and then deciding the best possible way to close the wound. In certain cases secondary intention healing or simple suturing is done, but in complex wounds reconstructive techniques to close the wound have to be employed, so as to secure anatomical, functional and cosmetic acceptability. So for this reason the reconstructive surgeons ascend the “reconstructive ladder” i.e. secondary intention, direct closure, skin graft, flap and tissue transfer to decide and follow the best way to proceed. Some of the techniques used in plastic surgery or reconstruction surgery are use of flaps and skin grafts, tissue expansion, tissue transfer; vacuum assisted closure and micro vascular surgery etc. The success of plastic surgery depends on secure and speedy wound healing, careful techniques, and consideration of blood supply and gentle handling of tissues⁴⁵.

Biologically based skin/tissue engineered skin substances have been developed and are now commercially available which overcome the limitations that include creation of the donor site, pain, scarring, infection and slow bleeding associated with autograf. The commercially available substitutes are Integra, Alloderm, Dermagraft and Apligraf^{46,47}. Integra is a dermal substitute that consists of bovine collagen; chondroitin-6-sulphate and silastic memberane. This is used as a dermal replacement for the treatment of third degree burn wounds⁴⁸. Apligraf is another important dermal substitute which is a bilayered living skin equivalent and is approved by US FDA. It is used in the treatment of various types of ulcers and surgical excision sites .it is considered safe and effective⁴⁹.

MODERN APPROCHES TO WOUND HEALING:**Gene therapy:**

Gene therapy is a new and emerging technology used for wound healing. It employs the process of manipulating genes to achieve a beneficial alteration in the gene product. Introduction of DNA or RNA molecules into the target cells is called gene transfer which could lead to alteration of the cellular functions i.e. inhibition or addition of the cellular function .It is a powerful tool to transfer potentially important proteins to the site of wound environment in high concentrations⁵⁰.

During wound healing the level of the growth factors has to be maintained as any increase or decrease in growth factors may lead to improper healing of the wound. Gene therapy is one of the approaches to regulate the amount of growth factors during the healing of the wound⁵¹. Delivery of the growth factors to the wound site is another important factor that effects wound healing, this can be effectively achieved by gene transfer^{52,53}. gene therapy also offers ways for the treatment of chronic wounds the possible advantages of which may be systemic or local regulation of gene expression, longer efficiency and lesser side effects⁵⁴.

Gene gun is a device that is used to deliver the gene to the site of the wound which makes use of the particle mediated bombardment technology. The advantages of using a gene gun may be its ability to target the projectiles to the different tissues and areas, stability of the DNA preparation, and ease and speed of the delivery vehicle. But its clinical application is restricted as tissue damage is caused by the impact of the particles⁵⁵.

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