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A REVIEW OF WOUND HEALING

HASSAN, A.Z.,* AMBER, E.I.,* AWASUM, C.A.,* REMI-ADEWUMI, B.D.,*[1] YILA, A.S., HASSAN, F.B.,*** AND JAHUN, B.M.****

*Veterinary Surgery and Medicine
**Veterinary Teaching Hospital
*** Division of Agricultural Colleges
Ahmadu Bello University Zaria

[1]**Correspondence**

SUMMARY

Wounds have been credited to be the most common and frequent reason for seeking medical attention. This review highlights the existing information on several aspects of wound healing. While the review presents the traditional information on wounds such as the etiology, classification and stages involved in wound healing, it attempts to capture the current information on hitherto obscure aspects of the healing phenomena, such as, the role of growth factors. Also reviewed are several traditionally used substances or clinical practices that are in fact, injurious to wounds.

KEY WORDS: A Review. Wound Healing

INTRODUCTION

A wound is a traumatic separation of the skin, mucus membrane or an organ surface and is a comm Key words: A Review. Wound Healing on and frequent reason for seeking medical attention (Hassan, 2002). Wounds are either simple, if no deeper tissues are involved or compound, when muscles, nerves, tendons and bones are involved. They have also been classified as incisions (cut) when produced by a sharp object, puncture if the object is pointed and narrow, lacerated if accompanied by tearing of tissues, contused if substantial amount of tissue is bruised and penetrating if the wound passes completely through a part of the body.

Wounds have also been classified based on the degree of contamination viz. clean, clean contaminated, contaminated and dirty wounds. Whereas clean wounds refer to surgical wounds created under aseptic conditions in which no contaminated or diseased tissue has been handled or incised, clean contaminated wounds are those created whenever surgical procedures involved entry into the gastrointestinal, genitourinary and respiratory tracts without significant spillage or when a minor break in asepsis occurs during an elective surgical procedure. Contaminated wounds are said to occur in traumatic wounds of less than 4 hours duration and in gross spillage from the gastrointestinal, genitourinary and respiratory tract during surgeries or a

major break in asepsis while dirty wounds are characterized by being traumatic wounds of greater than 4 hours duration, perforations of the gastrointestinal, genitourinary and respiratory tracts or when abscesses are lanced (Hassan, 2002). This review highlights the existing information on wound healing.

WOUND HEALING

Wound healing involves a complex series of cellular processes that are highly interdependent and overlapping. Macrophages are central to the initiation of the healing process as director cells (Wilson, 1997). Healing of wounds results in resurfacing, reconstruction and proportional restoration of its tensile strength. The response to injury has been divided into the early and late response. Whereas inflammation characterizes the early response, epithelization and maturation characterize the late response.

The early response commences when an injury is sustained and sequentially proceeds with hemorrhage, vasoconstriction, vasodilation, retraction and formation of platelet plugs elease of various clotting substances, dehydration of the clot and ultimately the formation of a scab. This is followed by the leakage of plasma enzymes, proteins, antibodies and complements. Cellular migration of leukocytes, red blood cells and platelets adhere to the vascular endothelium to commence the inflammatory phase.

Blood clotting is primarily due to the fibrin-fibrinolectin meshwork with adherent platelets. The fibrin plugs in damaged lymphatics on the other hand prevent spread of infection and the inflammatory response (Wilson, 1997).

The process of healing has been traditionally subdivided into the inflammatory, debridement, repair and maturation phases. Wound healing may also be by first or second intention (Hassan, 2002).

Inflammatory Phase

The inflammatory phase is considered to be a preparatory process for the formation of new tissue (Rapala, 1996). Coagulation, altered vascularity and inflammation, all of which modulate wound healing immediately follow wounding.

Coagulation is mediated by platelets and during thrombus formation, platelet factors that enhance fibroblast migration and proliferation are released. The normal inflammatory response occurs as small blood vessels dilate, capillary permeability increases, and peripheral neutrophils and then monocytes migrate into the wound. Monocytes are transformed into macrophages that phagocytize debris as well as enzymatically destroy bacteria.

Through the generation of bioactive substances, the macrophages initiate the complex processes of cellular proliferation and functional tissue regeneration. Cytokines produced by wound macrophages at the site of injury include; 1) chemo attractants that recruit and activate additional macrophages at the site of injury, 2) growth factors that promote cellular proliferation and protein synthesis, 3) proteases and extra-cellular matrix molecules, and 4) factors

that may restrain tissue growth once repair is completed (Dipietro, 1995).

Towards the end of inflammation, plasminogen activator is expressed in wound tissues and converts tissue plasminogen into plasmin, which digests the clot (Dipietro, 1995).

Debridement Phase

This follows the inflammatory phase and is evident within 24 hours following an injury. Phagocytosis is the process of recognition and engulfment of microorganisms or tissue debris that accumulate during infection, inflammation or wound repair. This ingestion, which is performed most efficiently by migrating, bone marrow-derived cells called 'professional phagocytes', is essential for successful host defense (Dipietro, 1995).

Repair Phase

Repair is a function of all living tissues. It commences within 12 hrs after an injury if the wound is clean and wound edges are apposed. It is characterized by migration of fibroblast, collagen formation, granulation tissue formation, wound contraction and epithelization (Dipietro, 1995).

i. **Fibroplasia**

It usually commences within 4 days of an injury and lasts for 2-3 weeks. This stage is signaled by the differentiation of the undifferentiated mesenchymal cells into fibroblasts facilitating collagen deposition and culminating in an increase in the strength of the wounded tissue (Badid *et al.*, 2000).

ii. **Collagen formation**

It is now known that there are several types of collagen and they are synthesized by fibroblasts, smooth muscles and epithelium. The most common, type I, make up the majority of skin, bone, and tendon. This macromolecular protein provides strength and integrity for all tissues. Cross-linking between the chains produces the fibril and subsequently the fiber.

After wounding, the rate of both collagen synthesis and degradation is altered so that enough collagen is synthesized, cross linked, deposited and removed to provide wound strength and integrity without excessive scaring (Lee and Swaim, 1988).

iii. **Granulation tissue formation**

Granulation tissue is composed of fibroblasts, capillaries, and collagen. Fibroblasts move into a wound by using the fibrin of the clot in the wound as a scaffold along which to grow. The new tissue formed by the fibroblasts and the bud-like capillaries constitutes what is commonly referred to as granulation tissue. Its functions are; to fill the space that has been created by the wound, to progressively reduce the size of an open wound by contraction, to function as a bacterial barrier (Lee and Swaim, 1988) and to provide a surface for the migration of epithelial cells (Badid *et al.*, 2000).

iv. **Wound contraction**

It is the concentric or centripetal reduction in wound size due to movement of fibroblasts in granulation tissue collagen and pulling forces of granulation tissue myofibroblast on wound edges (Lee and Swaim, 1988). The natural mechanism of wound contraction proceeds most rapidly if the wound is clean and free of infection. Wound contraction is however a biphasic phenomenon initially involving epidermal cells followed by the myofibroblasts (Baur *et al.*, 1981).

Wound contraction ceases when the wound edges meet due to contact inhibition of the cells or if the tension in the surrounding skin equals or exceeds the force of contraction before the wound edges meet as well as in the absence of myofibroblasts (Lee and Swaim, 1988).

v. **Epithelization**

This is the major healing phenomenon in the partial thickness wound and commences within 24 hours in incised and closed wounds but is delayed for about 7 days in full thickness open wounds requiring a granulation bed. The epithelial cells later differentiate and keratinize once several layers thick, resulting in a scar (Baur *et al.*, 1981).

Maturation Phase

This often takes several months or years after an injury and follows a decrease in Type 3 collagen and an increase in Type 1. There is also a reduction in the number of fibroblasts and re-orientation of collagen cross linkages. This collagen re-orientation is due to intermolecular and intramolecular cross-linking of the fibers. Scars formed are usually 15-20% weaker than the surrounding untraumatized tissue.

FACTORS AFFECTING WOUND HEALING

Beneficial Factors

i. **Topical wound mediators**

These are biological substances, the presence of which accelerates wound healing. The application of purified polypeptide growth factors, cytokines and matrix molecules has resulted in the acceleration of normal repair (Pierce and Mustoe, 1995). These mediators enhance wound healing by either enhancing activities of cells necessary for the initiation of healing or specifically enhance fibroblast and epithelia proliferation.

ii. **Proper antiseptic and antibiotic Use**

Disinfection of the skin around the wound is best initiated without contacting the wound itself. Povidone-iodine and chlorhexidine gluconate have emerged as the two agents of choice. However, antiseptics have been shown to be toxic to healing tissue, and should be cautiously used on open wounds (Cho and Lo, 1998). Concentrations of between 0.2% and 0.5% acetic acid and 0.5%

sodium hypochlorite (bleach) has been found to be beneficial in wound management (Amber and Swaim, 1984).

Antibiotics are recommended for wounds in which the magnitude of tissue injury is extensive. Fast wound penetrators are ampicillin, penicillin, the cephalosporins, and tetracycline. Those with relatively poor penetration into wounds include embecillin, nafecillin, oxacillin, gentamicin, erythromycin, and polymyxins (Clark, 1980). Though the intravenous route is preferred for antibiotic administration, the intramuscular route is also effective. Oral administration produces relatively low plasma levels (Clark, 1980). Topically, a combination of bacitracin, neomycin and polymyxin has proved useful in controlling wound infection.

iii. Nutrition

Protracted nutritional deprivation can manifest as immunocompromise and irreversible organ injury. Nutrients play a vital role in wound healing, they facilitate healing, maintain immune competence and decrease risk of infection. A balanced diet that consists of carbohydrates, protein, fat, vitamins and minerals is thus indicated in wounded individuals (Brylinsky, 1995).

iv. Good vascularity

Adequate blood flow ensures oxygen delivery to the wounded tissue, supply of phagocytes and humoral immune substances as well as nutrition and warmth all of which enhance wound healing (Suh and Hunt, 1998).

v. Growth factors

Growth factors are naturally occurring signal proteins (Hom, 1995) secreted by different cells or tissues and they play a very important role in accelerating the wound healing process. Growth factors stimulate fibroblast proliferation and chemotaxis, collagen synthesis, re-epithelization and angiogenesis. They are mainly released from macrophages, neutrophils, lymphocytes, platelets and fibroblasts and induce cells to migrate, divide or produce other factors required for wound healing (Hom, 1995).

Systemic growth factors, such as growth hormone and local epidermal growth factor (Chen *et al.*, 1995), fibroblast growth factor (Kawaguchi *et al.*, 1995; Bhora *et al.*, 1995, Okumura *et al.*, 1996), chemokines (Nanney *et al.*, 1995; McFadden and Kelvin, 1997), platelet-derived growth factor (Bartold and Raben, 1996; Beer, *et al.*, 1997), transforming growth factors (Pignatelli and Gilligan, 1996; Chen *et al.*, 1995; Wu *et al.*, 1997), epidermal growth factor (Ihn *et al.*, 1995; Guglietta and Sullivan, 1995), macrophage

migration inhibitory factor (Nishihira, 1998), lymphoid cells release soluble factors (Malinda *et al.*, 1998), keratinocyte growth factor (Werner and Munz, 1998), insulin-like growth factor (Schmid, 1995); Tsuboi *et al.*, 1995), macrophage colony-stimulating factor (Wu *et al.*, 1997), tissue-type plasminogen activator (Lotti and Benci, 1995) and connective tissue growth factor (Oemar and Luscher, 1997) have been shown to positively influence wound healing.

vi. Growth hormone

Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) are potent anabolic agents. Exogenous GH improves nitrogen metabolism in patients and tissue regeneration (Saito, 1998).

vii. Hyperbaric oxygen

Hyperbaric oxygen (HBO) therapy that involves exposing wounded tissue to hyperbaric oxygen in an enclosed chamber has been used as an adjunct to the treatment of non-healing wounds and it has been proved to speed up the healing process (Bykin, *et al.*, 1997).

Detrimental Factors

i. Malnutrition

Studies have shown that enhancement of wound healing was most prominent after 50 percent of weight loss had been restored while loss of a third of the body weight resulted in delayed wound healing (Demling and De-Santi. 1998).

In response to injury, the concentrations of several plasma proteins are characteristically altered. There is evidence that plasma proteins support tissue repair by metabolic as well as functional activity (Hassan, 2002). Specifically, plasma protein may directly facilitate wound healing by: provision of carbohydrates, lipids and amino acids in a usable form as biosynthetic precursors and energy substrates; the transport of trace metal cofactors involved in various wound repair processes; adhesion of regenerating tissue; modulation of the rate of structural protein synthesis; alignment of collagen subunits; organization of cellular elements in wound repair; prevention of autoimmune reactions; hormone transport and local modulation of hormonal effects; neutralization of the potentially toxic products of the inflammatory response and the inhibition of microbial invasion and colonization (Powanda and Moyer, 1981).

ii. Immune suppression

Wound healing represents a dynamic and immediate response of the body to tissue injury with the purpose of restoring anatomical continuity, structure and function. Success or failure of this complex cascade of events is determined largely by

competence of the host's immune system (Thornton, *et al.,* 1997).

Injury increase the levels of endogenous corticosteroids thereby affecting lymphocyte immune mechanisms leading to generalized immuno-suppression that, in turn, increases host susceptibility to infection and sepsis. Early resuscitation to restore lymphoctyye function after injury is important for tissue repair as both in vitro and in vivo studies have demonstrated that the presence of both macrophages and T-lymphocyes at the wound site are essential for the normal healing process to occur (Schaffer and Barbul., 1998).

iii. **Low oxygen tension**
Collagen synthesis is critically dependent on the availability of molecular oxygen to form the hydroxyprolyl and hydroxylysyl residues. Temporary anoxia may result in the formation of a less stable collagen resulting in fibers of low mechanical strength (Badid *et al.,* 2000).

iv. **Age**
Many of the processes involved in wound healing are impaired in the elderly. However, in elderly patients not suffering from concomitant diseases, the rate of wound healing is normal or only slightly reduced. Various 'systemic factors' (endocrine and hematological diseases, nutritional deficiencies and medications) as well as "regional disorders" (vascular and neural diseases) may impair wound healing. These complicating conditions occur more frequently in aged subjects (Van-de-Kerkhof *et al.,* 1994).

v. **Diabetes and other disease**
Impaired wound healing is a well-documented phenomenon in diabetes mellitus (Meyer, 1996). It has also been reported that wound-healing impairment in diabetes is due, at least in part, to a deficiency in growth factor activity within the wound environment (Bitar and Labbad, 1996).

Chronic diseases due to their catabolic activity, immuno-compromise and altered feed intake among others, all delay wound healing.

vi. **Steroid therapy**
Studies have shown that the use of glucocorticosteroids has detrimental effect on wound healing (Goforth and Gudas, 1980); Salmela, 1981). Glucocorticoids (corticosteroids) cause dehiscence of surgical incisions, increased risk of wound infection, and delayed healing of open wounds. They produce these effects by interfering with inflamation, fibroblast proliferation, collagen synthesis and degeneration, deposition of connective tissue ground substances, angiogenesis, wound contractration, and re-epithelialization. These actions are mediated by the antagonism

of various growth factors and cytokines (Anstead, 1998). These effects are most pronounced within the first 3 days of wounding but can be reversed by the administration of anabolic steroids.

vii. Cytotoxic drug treatment

Chemotherapeutic agents are known to impair wound healing. The extent of impairment by several agents (corticosteroids, adriamycin, methotrexate, and cyclophoshamide) is dependent upon the interval between administration and wounding. Most cytotoxic agents exert their antineoplastic effects by interfering with DNA replication, RNA production, Protein synthesis, or cell division. These effects influence the healing wound by inhibiting collagen formation (Lee and Swaim, 1988).

These drugs are also credited to cause neutropenia due to their cytotoxicity, which further potentiates wound infection. These effects are most pronounced if administered within the first 7 days of wounding (Hassan, 2002).

viii. Stress

The impact of stress on wound healing is due to the reduction in inflammation and delayed healing correlated with increased serum corticosterone levels (Padgett, *et al.,* 1998).

ix. Concentrated antiseptics

Wound antiseptics of different types are widely used in first aid treatment to counteract wound infection and several antiseptics at high concentrations are known to impair healing (Amber and Swaim, 1984).

x. Infection

Clinical wounds are of necessity contaminated, however, only a few of these wounds result in infections. Wound infection has three main constituents: (1) bacterial inoculum, (2) bacterial nutrition, and (3) impaired host resistance.

The risk of wound infection varies according to the following equation:

$$\text{Probability of infection} = \frac{\text{Dose of Bacterial Contamination} \times \text{Virulence}}{\text{Resistance of the Host}}$$

Infection not only elicits a systemic septic response but actually inhibits the multiple processes involved in the wound-healing scheme.

Presence of devitalized tissue strongly enhances wound infection. The devitalized tissue achieves this by acting as a culture media for the bacteria and also through inhibition of leukocyte phagocytosis by decreasing the oxygen tension (Dipietro, 1995).

xi. Zinc deficiency

Its deficiency results in skin changes, poor appetite, mental lethargy, neurosensory disorders, and cell-mediated immune disorders all of which delay wound healing (Prasad, 1995).

xii. **Vitamin A, C and K deficiency**
A nutritionally complete diet provides the optimum environment for recovery and healing. Clinical research and experience suggest that several nutritional factors may also be associated with impaired wound healing, including vitamin C, vitamin A, vitamin E, protein and individual amino acids (Thomas, 1997).

xiii. **Foreign bodies**
Specific infection potentiating fractions have been identified in the soil, which include its organic components as well as its inorganic clay fractions. The negatively charged clay particles are absorbed into leukocytes inhibiting their phagocytic activity as well as inhibiting the antibacterial serum factor properdin. Clay has also been established to inactivate basic antibiotics such as gentamycin, kanamycin, streptomycin and neomycin.

Likewise the use of various drains and sutures have retarded wound healing primarily or secondarily be increasing the likelihood of wound infection. While the volume of suture has a direct effect on the magnitude of potentiation of wound infection, absorbable and braided natural sutures also impact negatively on wound healing (Ihn *et al.*, 1995).

xiv. **Radiation**
Irradiation complicates tissue repair and surgical wound healing. First, the early phase inflammatory response is severely inhibited. In particular, the number of infiltrating macrophages and neutrophils is decreased, blood vessels are injured and hemorrhage becomes evident. Secondly, the formation and maturation of granulation tissue are slowed down while fibroblasts are injured and transcription of genes and collagen mRNAs is hampered. Synthesis and secretion of collagen are consequently reduced (Tibbs, 1997).

xv. **Local anesthetics**
Local anesthetics have effects on wound healing. In experimental studies, procaine at high concentrations has been proved to retard healing. Other studies have shown that lidocaine and bupivacaine inhibit collagen synthesis in fibrobalst tissue cultures. Likewise local infiltration and topical application of lidocaine produced significant histopathologic changes in healing wound (Eriksson and Sinclair, 1996; Drucker *et al.*, 1998). This is due to their ability to decrease synthesis of proteins, secretion of plasma proteins, histamine release from mast cells as well decreased collagen synthesis.

xvi. **Others**
Vasoconstrictors, such as epinephrine when used as adjuncts to anesthetic agents injected directly into the wound also exert deleterious effects on

tissue defenses and potentiate wound infection.

The administration or application of several preparations or conditions negatively impact on the healing process. These conditions include obstructive jaundice (Dawiskiba *et al.,* 2000), the production of tumor necrosis factor-alpha (Kawaguchi *et al.,* 1995), thermal damage (Sanders and Reinisch, 2000) as well as the use of various immunosuppressants such as tacrolimus. Damage to the local nerve supply also retards cutanous wound healing by interfering with neurogenic inflammation (Schaffer *et al.,* 1998). Disruption of healing wounds also retards healing. This may be due to undue tension on wounds, mobility at wound edge, poor suture selection and technique, tissue necrosis, ischemia, hematoma and infections.

COMPLICATIONS OF WOUND HEALING

Complications of wound healing are associated with:

i. The presence of dead or dying tissue.
ii. Infection.
iii. Mechanical factors (e.g. Constant tearing of newly formed elements in wounds at the flexor and extensor aspects of joints or excessive scratching or licking of the wound or due to incorrectly applied dressings or bandages).
iv. The anatomical site (e.g. one with a poor blood supply as for instance over superficial bone or when there is likely to be repeated injury such as over-reaching or brushing).
v. The presence of an alien tissue (e.g. Serous membrane or omentum in a penetrating skin wound).
vi. The existence of foreign bodies, either animate (e.g. Parasites) or inanimate, these latter may be extrinsic such as grit or wood splinters, or endogenous, such as detached bone chips).
vii. Tumor cells invading the wound.
viii. Imbalance between connective tissue and epidermal healing rates.
ix. Persistent irritation and major trauma elsewhere. Disruption and destruction of the basement membrane are characteristic of wounds that are slow or fail to heal resulting in ulcers (Hopkinson *et al.,* 1997). Management of local and systemic co-factors that delay wound healing will mitigate their adverse effects and facilitate healing of the individual's chronic wound (Stotts and Wipke-Tevis, 1996). Other complications of the healing process are self-mutilation, various contractures and exuberant fibrous or granulation tissue (Oemar and Luscher, 1997).

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