HEALING OF ORAL WOUNDS AND REGENERATION OF TISSUE: A REVIEW ARTICLE

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Abstract

The present study focuses on the healing of wounds in oral cavity and regeneration of oral tissues. It includes the proper mechanism of healing to devise required treatment that promotes healing of wound in minimum amount of time and to avoid any complication arising from improper healing. The mechanism of wound healing is a complex physiological process, which is facilitated by certain local and general factors. The study also provides descriptive representation of the phases of wound healing. The study aims to provide the knowledge and skills that can help in identifying patients at risk for development of wounds and complications arising during healing of wounds.

Introduction

Wound healing is a self-mechanism. Wound healing is a process which includes several phases and comprises of sequential of complex biological process. All local tissues participate in the process and results with minimal scar formation. In case of oral wounds, wound healing occurs in warm oral fluid containing millions of microorganisms. There is no scar formation in the wound healing of oral cavity, rather, there is formation of trismus, which is formed histologically from normal connective tissue under epithelial cells. Many local and general factors enhance the process[1].

The present review attempts to focus on the phases of wound healing. The study is required to develop proper preventive measures to promote wound integrity and to treat wound problems and complications if and when they arrive. Revealing the basic mechanisms in the healing process and then regulating these processes for faster healing or to avoid negative outcomes such as infection or scarring are fundamental to wound research. The normal healing process is basically known, but to thoroughly understand the very complex aspects involved, it is necessary to characterize the course of events at a higher resolution with the latest molecular techniques and methodologies[1]. The National Institute of Dental Research (NIDR) also invites investigation initiated grant applications to conduct detailed clinical research on wound healing and tissue regeneration associated with orofacial region. This promotes learning and motivates young minds to take initiative in developing faster and better techniques and equipment to achieve complete and healthy wound healing[2].

Materials and Methods-

The present review article is summarized after surveying various Books and literature across the internet. It was an attempt to an analytical study, which was performed to collect proper knowledge on all aspects of wound healing. Basic information about the types of wounds and their classification, as well as factors affecting wound healing was acquired by referring to various textbooks like "Textbook of oral pathology by B Sivapathasundharam" and "Pathological Basis of Disease by Robbins and Cotran". Anonymous Patient records provided in several literatures were studied and thoroughly analyzed to assess the time taken by various wounds to heal. Complications arising during the healing of wounds were reviewed**.** Most helpful article describing the need for studying wound healing and the methods that are currently being used for the said purpose was the study carried by Nutila et al (2014)[3].

Statistical studies regarding the complications arising during wound healing were also considered. It was evident that many advances are now being made in the study of wound healing. Earlier animal models were the prime source for experimentation and analysis of wound healing. Rodents and pigs were the ideal models to be used for study due to pre-existing methodologies as well as low maintenance and ethical ramifications concerning these animals[3]. However, the species specific misinformation occurred in the studies due to different genetic makeup and habituating conditions of these animals. So, a more human directed study was required for efficient analysis. Fortunately techniques like PCR, RNA sequencing etc. are developed which only require a fragment of patient's skin to provide complete information regarding different gene expressions and how they are altered in trauma or disease.

Results-

The healing of wounds is a complex but remarkable process which is susceptible to interruption due to various local and systemic factors that include local factors like moisture, mechanical injury, infection, oedema , maceration, ischemia etc., as well as systemic factors like age of the patient, hormonal factors, body type, nutritional factors, other pathological conditions etc. When the right healing atmosphere is established, the body has the capacity to heal and replace devitalized tissues.

A wound is a circumscribed injury caused by any external force, physical or chemical on any tissue or organ of the body. Wounds can be classified into various categories based on their origin, depth and contamination. Healing of wounds is a process that involves wound contraction ascribed at least in part to myofibroblasts (altered fibroblasts with characteristics of smooth muscle fibres ultra-structurally). This contraction causes reduction in the size of the wound and its consequent replacement by healthy tissue in the following weeks. This replacement is carried out by mitotic division and migration of surrounding cells. Replacement of lost tissue by granulation tissue is termed as **repair** which results in scarring and replacement by similar type of tissue known as **regeneration**[4]**.**

The study of wound healing and tissue regeneration concluded that healing is a phase of inflammatory reaction because it cannot be separated from the vascular and cellular changes occurring in response to an injury. Wound healing requires multiple finely tuned processes that occur in a specific sequence. Intact homeostatic and inflammatory mechanisms are needed, and the mesenchymal cells must migrate to the wounded area and proliferate at site of injury[5]. Whereas, at the edges of the wound are approximated, the healing is fast and is known as healing by first intention or primary intention, whereas when there is tissue loss and the wound cannot be opposed, it contracts to reduce size, the granulation tissue fills the wound and epithelialization occurs across wound surface. This is called as healing by secondary intention[6].

From the onset of injury the body is set into motion by an automatic series of events known as the cascade of healing. From the information compiled from various sources it can be concluded that the cascade of healing occurs in four different phases- Haemostasis phase, Inflammatory phase, Proliferation phase, and Maturation phase[7].

1. **Phase 1- Haemostasis Phase**
   The objective of this phase is to stop the bleeding which occurs from the onset of injury. The blood clotting system is activated which forms a dam like structure to stop the bleeding. Platelets come in contact with collagen, which results in their activation and they accumulate at the site of injury. A mesh of fibrin fibres is formed with the help of thrombin enzyme which in turn clumps the platelets to form a stable clot.
2. **Phase 2- Inflammatory phase**
   In this phase neutrophils enter the wound to destroy the bacteria accumulating in the wound and to remove dead tissue and other debris. As the WBCs leave, specialised cells like the macrophages continue the cleaning process and secrete specialised growth factors and proteins that attract immune system cells to the wound to facilitate repair[8].
3. **Phase 3- Proliferative Phase**
   It features three distinct stages-
   a. Filling of wound
   b. Contraction of wound healing
   c. Covering the wound i.e. epithelialisation.

   A shiny, deep red granulation tissue fills the wound bed with connective tissue, and new blood vessels are formed. Wound margins contract and epithelial cells arise from the wound bed and migrate across the wound bed until the wound is covered[8].
4. **Phase 4- Maturation Phase**
   The new tissue gains strength and flexibility. Collagen fibres reorganize and the tissue remodels and matures.

By the research conducted for this literature, it can be deduced that within the wound healing process, the inflammatory phase involving haemostasis and inflammation, starts with the onset of injury and continues for about 4 to 6 days. The proliferation phase involving the epithelialisation, angiogenesis, granulation tissue formation, and collagen deposition, usually starts from day 4 and continue till day 14 after injury. Epithelial cells migration starts after mere 24 hours while the maturation and remodelling phase starts from day 8 after injury and proceeds for about a year[5, 9,10].

Significant Tables-

Table 1- Difference between primary and secondary healing[7]

FEATURES	PRIMARY HEALING	SECONDARY HEALING
1. Cleanliness	Clean	Not Clean
2. Infection	Not infected	Infected
3. Margins	Surgically clean	Irregular
4. Sutures	Used	Not used
5. Healing	Small granulation tissue	Large granulation tissue
6. Outcome	Linear scar	Irregular wound
7. Complications	Not frequent	Frequent

Table 2- Local and General Factors that contribute to disturbed wound healing[5]

LOCAL FACTORS	GENERAL FACTORS
Wound size	Hereditary defects of wound healing
Wound localization	Nutritional deficiency
Postoperative bleeding	HIV
Thermal damage	Cancer
Perforation to the maxillary sinus	Old age
Sharp bone edges	Diabetes
Local anaesthetics	Jaundice
Infection	Alcoholism
Hypo-perfusion	Uraemia
Ischemia	Immunosuppressive therapy
Foreign bodies	Corticosteroids
Smoking	Chemotherapeutics
Venous insufficiency	Antiresorptive medication
Mechanical trauma	Other medication
Local toxins	Vitamin A
Head or neck irradiation	Hypothyroidism
Cancer of oral cavity	Hyperbaric oxygen
Presence of necrotic tissue	Anaemia
Local stem cell injections	
Underlying pathological fractures	
Injudicious flap design in surgery	
Oedema	
Pathological mobility	
Tooth in the line of a jaw fracture	
Traumatic occlusion	

Schematic Representation of Wound Healing[11]-

Injury	After 4 days	After 20 days	Wound closure
Haemostasis ✓ Damaged vessels constrict to slow blood flow. ✓ Platelets aggregate to stop the bleeding. ✓ Leucocytes migrate into tissue to initiate inflammatory process.	Inflammation • Neutrophils secrete chemicals to kill bacteria. • Macrophages engulf and digest foreign particles and necrotic debris. • Macrophages release angiogenic substances to stimulate capillary growth and the granulation process.	Proliferation • Fibroblasts proliferate in the wound and secrete glycoprotein and collagen. • Epidermal cells migrate from wound edge. • Granulation tissue is formed from macrophages, fibroblasts and new capillaries.	Remodelling • Fibroblasts secrete collagen to strengthen the clotted wound. • Wound remodelling occurs to recognize fibres. • Wound contracts increasing tissue integrity. • Epidermal cells grow over connective tissue to close wound.

Discussion-

❖ **Healing of extracted wound**

After the removal of a tooth, the blood filling the socket coagulates, RBCs entrap in fibrin meshwork and the ends of the torn vasculature in the periodontal ligament are sealed off. There is vasodilatation and engorgement of blood vessels in the remnants of the periodontal ligament and mobilisation of leucocytes to the area around the clot[7].

✓ **First week wound**

Within the first week after tooth extraction, proliferation of fibroblasts from connective tissue cells in the remnants of the periodontal ligament is evident and these fibroblasts grow into the clot around the wound. It is a temporary structure which is to be replaced by granulation tissue. The crest of the alveolar bone begins to exhibit osteoclastic activity and a thick layer of leucocytes converge over the clot and the wound continues to exhibit epithelial proliferation[6].

✓ **Second week wound**

During the second week after extraction, the blood clot becomes organised by fibroblasts growing into the clot on the fibrin meshwork. Angiogenesis takes place and the newly formed capillaries penetrate the centre of the clot. Periodontal ligament remnants undergo degeneration and the margins of the alveolar bone exhibits marked osteoclastic resorption[4].

✓ **Third week wound**

Trabeculae of osteoid or uncalcified bone are formed around the entire periphery of wound with progression of healing. This early bone is formed by osteoblasts which are in turn derived from pluripotent cells of the periodontal ligament assuming the osteogenic function.

The cortical bone of the socket undergoes remodelling and the crest of alveolar bone gets rounded off due to osteoclastic resorption. Now the wound is completely reepithelialised[9].

- ✓ **Fourth week wound**

  The wound enters the final stage of healing. There is continuous remodelling of the bone of the socket with reepithelialisation of tissue. The bone now completely fills the socket and the crest gets rounded off[4].

- ○ Complications arising in healing of extraction wounds.

  The major complications with healing of fibrous socket are listed as dry socket and fibrosis of the healing socket.

❖ **Healing of the palate.**

The healing of the palate and the surrounding gingival tissue occurs without any scar tissue formation when the healthy underlying bone is present. This is due to early onset of the inflammatory phase, decreased levels of immunity mediators, fewer blood vessels, and more cells originating from the bone marrow, rapid re-epithelialisation, and rapid fibroblast proliferation[5]. However, in the absence of healthy underlying bone, the healing is much more complex and is accompanied by heavy scarring and even perforations to the nose and sinus. This is usually observed in the patients who have undergone surgery for cleft palates.

❖ **Healing of the pulp**

Healing of dental pulp depends on the degree of infection and pulpal inflammation, amount of tissue involved and the age of the patient[4]. Healing relies on preservation of blood supply and survival of the odontoblastic layer[5]. In the event of survival of odontoblastic layer, the cells differentiate and form reactionary dentin. The stem cells or progenitor cells of the pulp differentiate into odontoblasts to form reparative dentin. However, prolonged inflammation can lead to pulpal necrosis.

❖ **Healing of jawbone fracture**

Jawbone fractures heal similar to the healing of dermal wounds in many aspects. Fracture can heal by either primary or secondary intention. Direct bone healing or healing by primary intention occurs when there is pre-existing stable fixation of bone fragments and good blood supply. There is no callus formation in direct bone healing while Bone healing by secondary intention or indirect bone healing is characterised by callus formation. It occurs in stages with the first stage being the formation of haematoma or blood clot at the fracture site containing the fragments of bone as well as the devitalised tissue. The second stage is characterised by liquefaction and degradation of nonviable tissue. Soft callus is formed in the third stage which bridges the gap between the fractured segments of bone. This soft callus is then mineralised and converted to bone. This is known as the fourth stage. Remodelling of bone occurs and the excess of callus is resorbed. The bone marrow is recanalised.

❖ **Complications of disturbed wound healing**

- Infections- Wounds are a portal of entry of a large amount of microorganisms that can cause severe harm to the body and can also delay the healing process.
- Keloids and hypertrophic scar formation- Keloids are overgrown scar tissues that are rarely resolved. They are mostly seen in wounds with normal but delayed healing. They mainly occur due to increased synthesis of collagen by fibroblasts.
- Pigmentary changes- These are usually found on the dermal wounds. It may appear hypo-pigmented or hyper-pigmented.
- Implantations Cysts- These are cysts formed when epithelial cells get entrapped in the wound and proliferates later on.

❖ **Systemic medications affecting wound healing**

Following drugs affect wound healing-

1. Bisphosphonates.
2. Glucocorticoids.
3. NSAIDS
4. Cyclooxygenase-2 inhibitors.

Conclusion-

Understanding of wound healing is as important as knowing the pathogenesis of disease because satisfactory wound healing is the ultimate goal of treatment. Various approaches and methods can be designed based on the knowledge of wound healing to successfully avoid and overcome all the complications arising with the injury. Drugs and treatments can be effectively determined by studying the mechanism of wound healing and inspecting the wound. Wound healing in mouth occurs despite the excessive bacterial and viral load but the complications when they arise can be very severe. So thorough knowledge and judicious examination of the wounds is very crucial to devising the appropriate treatment plan.

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