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Healing Process on the Oral Traumatic Ulcer (OTU): A Review

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Abstract

Background

Oral and dental health is a very important part for humans. Basic Health Research in 2018 showed that the prevalence of dental and oral problems in Indonesia still reached 45.3%. In Indonesia, the incidence of oral traumatic ulcers is 93.3% when compared to other oral lesions. Oral traumatic ulcers are often painful and appear as erythematous, raised edges with yellowish-white necrotic pseudomembranes that can be easily removed, and can occur on the buccal mucosa, tongue, and lower lip.

Purpose

This paper aims to explain the healing process of oral traumatic ulcers.

Discussion

Oral traumatic ulcer or OTU is a lesion condition in the oral cavity induced by trauma, either chemically, thermally, electrically, or mechanically. The key of treating oral traumatic ulcers is finding and eliminating the etiology of traumatic ulcers. The wound healing is divided into four stages, including hemostasis, inflammation, proliferation, and remodeling. The various stages that accompany the wound healing process can occur faster than the cycle that should occur through the induction of various anti-inflammatory substances, such as flavonoids, phenols, tannins.

Conclusion

It is important to understand the healing process of oral traumatic ulcers so that they do not develop into chronic wounds.

Keywords: Oral Traumatic Ulcer, Etiology, Clinical Sign, Healing Process, Good Health and Well Being

Introduction

Oral and dental health is an important part for humans. Basic Health Research in 2018 showed that the prevalence of dental and oral problems in Indonesia reached 45.3% (Riskesdas RI 2018, p.182). One of the complaints of oral disease that can be found in the world is oral lesions. Common oral disorders in the population, oral ulcers are characterised by the loss of connective tissue in the base layer along with the ongoing degradation and deficiencies in the mouth epithelium. Oral ulcers have a variety of etiological reasons, including trauma, infections, allergies, skin conditions, autoimmune illnesses, tumours, and more (Zeng *et al*., 2022, pp. 1-2) [74].

Trauma or injury to the mucosal tissue can lead to the formation of oral traumatic ulcers. These are typically single lesions in the mouth caused primarily by trauma. The trauma may be mechanical, such as irritation from removable dentures, or chemical, and often affects areas prone to injury like the lips, oral mucosa, or regions near denture clasps. Other common sources of trauma include cracked teeth, sharp tooth cusps, or components of dental appliances (Rawlings & Willis, 2023, pp.

101-105) [48]. In Indonesia, the incidence of oral traumatic ulcers is 93.3% when compared to other oral lesions (Sa'adah *et al*., 2020, p. 11; Soares *et al*., 2023, p. 1). Based on research conducted by Owczarek-Drabińska *et al*. (2022), 4.2% of the population aged 1 day to 17 years in southwestern Poland experienced oral traumatic ulcers. The results of a study conducted in Shanghai, China on a population aged 17 to 92 years showed that 1.23% of the population experienced oral traumatic ulcers (Ge *et al*., 2020, p. 4). Meanwhile, in Indonesia, the results of a study conducted on a population aged 5 to 55 years showed that 6.7% of the population experienced oral traumatic ulcers (Amtha, Marcia, and Aninda, 2017, p. 71). This condition can be exacerbated by the dynamic oral cavity environment, so treatment is needed that can reduce pain, inflammation, and accelerate healing (Moussa *et al*., 2023, p. 2).

Clinically, oral traumatic ulcers are characterized by damage to the epithelial layer that reaches the supporting tissue with clear boundaries forming a depression (Mortazafi *et al*., 2016, pp. 7-8; Thakrar & Chaudhry, 2016, pp. 30-33) [36, 62]. Oral traumatic ulcers are usually painful and present as red lesions with raised borders and a yellowish-white necrotic pseudomembrane that can be easily wiped away. These ulcers commonly develop on the buccal mucosa, tongue, and lower lip. Their symptoms can interfere with a patient's daily activities, making appropriate treatment essential for effective healing (Minhas *et al*., 2019, pp. 3344-3345) [35]. Management of oral ulcers can be done by eliminating causative factors, such as sources of trauma, the use of topical drugs such as local anesthesia sprays and topical corticosteroids (Rawlings & Willis, 2023, pp. 101-103) [48]. This paper aims to explain the healing process of oral traumatic ulcers.

Oral Mucosa

The oral mucosal tissue is composed of several layers: Stratified squamous epithelium, basement membrane, lamina propria, and submucosa, as illustrated in Fig 1. This tissue is covered by a gel layer primarily made up of inorganic salts—mainly secreted by the sublingual salivary glands—and mucin, a highly glycosylated protein. The gel acts as a protective and lubricating barrier, with a thickness ranging from 40 to 300 µm. Additionally, a saliva layer about 70 µm thick coats the mucosa. The epithelial thickness varies based on the degree of keratinization, with the thinnest epithelium located on the floor of the mouth. In healthy tissue, the epithelium typically contains 40 to 50 cell layers and has an average thickness of 294 ± 68 µm (Edmans *et al*., 2020, pp. 2-3).

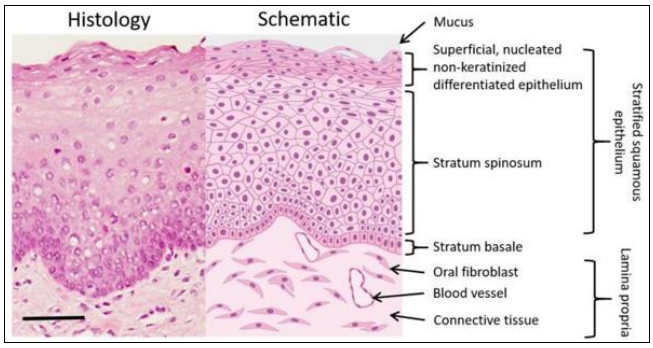

Fig 1: Schematic design (right) and histological depiction (left) of the buccal mucosa of the oral cavity (Edmans *et al*., 2020, pp. 2-3)

Oral mucosal tissue has many similarities in structure with the skin. Both consist of stratified epithelium containing melanocytes, keratinocytes, Langerhans cells, and Merkel cells that function as protection against microbial invasion and loss of body fluids. However, histologically, the oral mucosal tissue and skin tissue have differences that can be seen in Fig 2. This image is done using stainingHematoxylin And Eosin on tissue sections incubated in paraffin with a thickness of 5 µm on a 100 µm scale bar (Waasdorp *et al*., 2021, pp. 2-3).

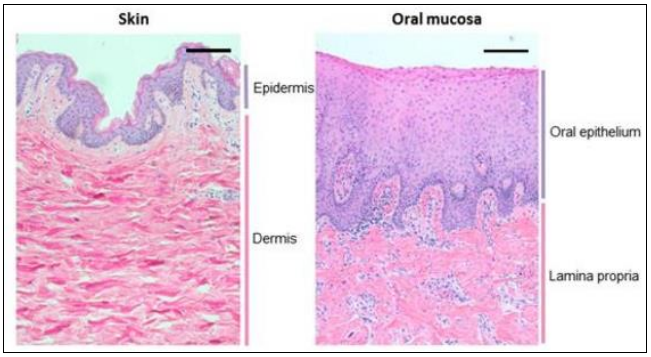

Fig 2: Histology of oral mucosal tissue (right) and skin tissue (left) (Waasdorp *et al*., 2021, p. 3)

The epithelial layer of the oral mucosa differs in thickness from the epidermis of the skin, with the oral mucosa being generally thicker. In comparison to the skin, the basal membrane has more cell layers and more cell proliferation, especially in the palatal and buccal mucosa, which accounts for the increased thickness. Additionally, the entire skin epidermis is keratinized, whereas the oral epithelium includes both keratinized and non-keratinized regions. For example, the buccal mucosa is non-keratinized, allowing it to be more flexible and better able to absorb compressive forces. In contrast, the epithelium of the hard palate and gingiva is keratinized, providing resistance to mechanical stress during chewing (Waasdorp *et al*., 2021, p. 3).

Under the skin's epidermis and the oral mucosa's epithelial l ayer, connective tissue provides support both structurally and nutritionally needed for regeneration. This layer is known as the dermis in the skin and the lamina propria in the oral mucosa. As in Fig 3, the connective tissue layer contains fibroblasts, mast cells, macrophages, and other supporting cells embedded in the extracellular matrix. In both the lamina propria and dermis, the extracellular matrix consists mostly of type I collagen and type III collagen with a ratio of 5:1. The extracellular matrix in non-keratinized epithelium has a looser structure and more elastin when compared to keratinized epithelium and skin. The connective tissue layer, which contains adipose stem cells and progenitors, sits above the adipose tissue layer in the skin and buccal mucosa, but in the palate's hard part and gum tissue, it is directly connected to the bone via the mucoperiosteum (Waasdorp *et al*., 2021, p. 4).

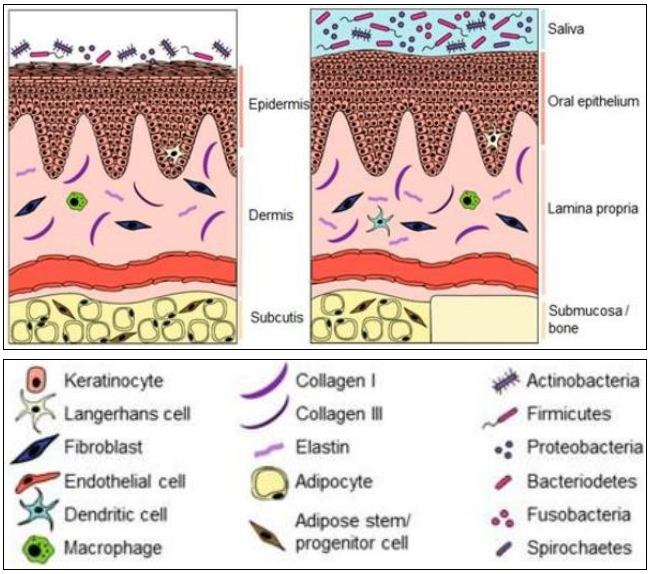

Fig 3: Cell types in oral mucosal tissue (right) and skin tissue (left) (Waasdorp *et al*., 2021, p. 3)

Oral Traumatic Ulcer

Oral traumatic ulcer is a lesion of the oral cavity caused by trauma. There are numerous etiological reasons that can lead to oral traumatic ulcers, including mechanical, chemical, electrical, or thermal trauma, both acute and chronic (Wang *et al*., 2022, pp. 204-205; Fitzpatrick *et al*., 2019, p. 97) [67, 20]. The duration of these oral traumatic ulcers might range from a few days to many weeks.

Three days after the damage heals, oral traumatic ulcers are typically painless and will go away in ten days. However, these lesions may last for a few days or even weeks because of the tissue's repetitive damage (Rosa *et al*., 2023) [53]. Within 14 days, acute traumatic ulcers typically heal without any problems. However, a biopsy is required to determine whether neoplasia or other diseases are present because persistent ulcers may not show a clear source of damage (Fitzpatrick *et al*., 2019, p. 97) [20].

Chronic ulceration that does not heal will be trapped in a prolonged inflammatory cycle and fail to proceed to normal healing development. Therefore, inflammatory cell infiltration following inflammatory cytokine levels are necessary for ulcer wound healing and tissue restoration (Wang *et al*., 2022, p. 204) [67].

Etiology

Lesions that result in the loss of the epithelial layer above the basement membrane are known as oral traumatic ulcers. The tongue, buccal, labial, and gingival mucosa can all develop oral traumatic ulcers. The buccal and labial mucosa are where these ulcerations most frequently appear (Glick, 2015, p. 663; Liang *et al*., 2024, p. 2; Moussa *et al*., 2023, p. 2).

Oral traumatic ulcers cause severe pain, impaired eating function, impaired drinking function, and impaired speech function. These conditions can cause decreased quality of life and efficiency in activities. In addition, oral traumatic ulcers also have a risk of malignancy (Liang *et al*., 2024, p. 2; Moussa *et al*., 2023, p. 2).

Oral traumatic ulcers can be caused by several traumas such as thermal trauma, mechanical trauma, chemical trauma, and electrical trauma. Some of these types of trauma can consist of several things that are often encountered in daily dental practice. Dental materials like restorative materials, local anaesthetics, sodium hypochlorite, formocresol, topical use aspirin, topical products for oral hygiene like hydrogen peroxide, prosthetic cleansers, and mouthwashes, along with the use of illegal drugs like cocaine, amphetamines, and methylenedioxymethamphetamine (MDMA), are all linked to oral traumatic ulcers brought on by chemical trauma (Fitzpatrick, 2019, p. 97) [20]. In addition, the consumption of drugs by sucking or chewing which should be swallowed directly, such as oral bisphosphonates or aspirin. In addition, the use of mouthwash with high concentrations of alcohol content that is used too often or without dilution (Glick, 2015, pp. 86-87).

Contact with high-temperature materials and extremely cold temperatures, including touching frozen metallic material, dried ice, or nitrogen liquid, are the most common causes of thermal trauma that can result in oral traumatic ulcers in tissue. Thermal trauma typically affects the roof of the mouth and the front part of the tongue and is caused by hot food or beverages, particularly those that have been microwaved. Another cause of thermal trauma is the use of e-cigarettes which have the potential to injure the oral cavity if they explode (Fitzpatrick, 2019, p. 97) [20].

Acute or chronic oral traumatic ulcers can result from mechanical stress. Tooth malposition, diastema, fractured or sharp teeth, prostheses (sharp or rough dentures, broken retainers, unstable dentures) or functional (unstable tongue position, biting, or sucking the lips/cheeks/tongue) and rough or sharp fillings are a few mechanical factors. In general, after the mechanical cause is removed or corrected, oral traumatic ulcers can heal (Pantenero *et al*., 2022, p. 2111; Wijayanthy & Sidiqa, 2022, pp. 204-205 [70]; Yamada *et al*., 2020, p. 2020) [72].

Oral traumatic ulcers can also appear due to*factitious habits*, which is a habit that is often done unconsciously until it causes health problems. Examples of such habits are biting the lips, cheeks, or tongue which causes trauma to the mucosa in the oral cavity. In addition, motor dysfunction, sharp teeth, hard foods, irritation due to poor restorations, and ill-fitting devices are also causes of*oral traumatic ulcer* (Glick, 2015, pp. 663-664; Yogarajah *and* Setterfield, 2021, p. 407).

Clinical Symptoms

Oral traumatic ulcers have clinical features with forms that depend on their etiology. However, oral traumatic ulcers generally have a yellowish lesion base. The edges of the lesion are reddish/erythematous and raised with a yellowish-white or grayish-white necrotic pseudomembrane, and a smooth ulcer surface (Wijayanthy & Sidiqa, 2022, pp. 204-205) [70].

These ulcers are often found in areas around traumatic agents, such as orthodontic appliances, sharp teeth, or sharp restorations. Oral traumatic ulcers usually occur on non-keratinized areas, including the gingiva, lips, buccal and labial mucosa, hard palate, and soft palate. and lateral edges of the tongue (Moussa *et al*., 2023, p.2). The duration of oral traumatic ulcers can range from days to weeks but generally heal within a few days (Wijayanthy & Sidiqa, 2022, pp. 204-205) [70].

The extent of oral traumatic ulcers is influenced by the cause of the trauma and the location of the trauma depends on the activity involved. In high-heat electrical burns, oral traumatic ulcers are quite large, involve the lips, and usually

occur in young children and toddlers. In contrast to high-heat electrical burns, burns from hot food and drinks are generally small and localized to the hard palate mucosa or the lips and are usually seen in adolescents to adults (Glick, 2015, p. 87).

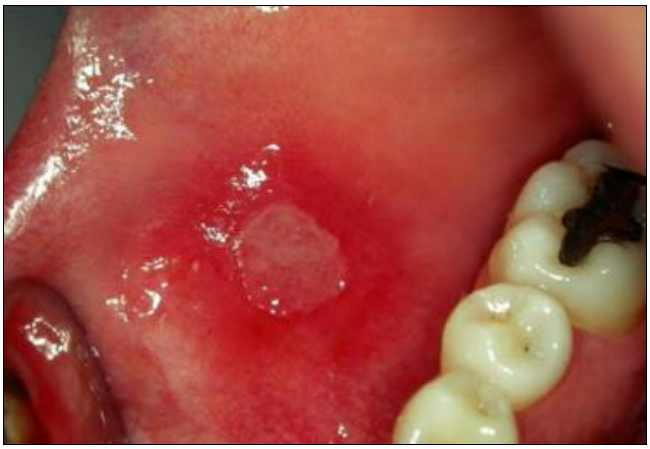

Fig 4: Clinical features of oral traumatic ulcers (Tremolati *et al*., 2022, p. 761) [64]

Pathophysiology

Oral traumatic ulcers arise due to trauma that causes tissue damage in the oral cavity. The emergence of ulcers is a response of the oral mucosal tissue to injury from either local or systemic factors. A patient's oral cavity may become uncomfortable if they have long-term damage from mechanical, thermal, and chemical stress (Gasmi *et al*., 2021, p. 1158) [21].

The pathophysiology of oral traumatic ulcers depends on the cause of the trauma involved. Oral traumatic ulcers caused by high-heat electrical burns begin with lesions that appear charred and dry. After a few days, the charred and dry structure peels off and allows excessive bleeding of the involved oral mucosa. Oral traumatic ulcers in burns due to hot food or drinks will appear as a reddish area that will develop into oral traumatic ulcers after a few hours of trauma. The healing time of oral traumatic ulcers depends on the area involved (Glick, 2015, p. 87).

Once an oral traumatic ulcer forms, damage to the epithelial layer, which protects the oral mucosa, allows bacteria to enter the wound area. This condition will increase the severity of the oral traumatic ulcer and can slow down the healing process. In addition, bacteria that enter the wound area can cause secondary infections by affecting health systemically (Liang *et al*., 2024, p. 2).

The first step in the pathophysiological process of oral traum atic ulcers is tissue damage in the mouth cavity. Vascular an d cellular reactions can be brought on by traumatic injury.

This can lead to inflammation around the traumatized tissue. The effects of inflammation include increased temperature in the area around the trauma, swelling or increased tissue volume (Dermawan *et al*., 2022, p. 76) [15].

The vascular response of traumatized tissue is in the form of vasodilation of blood vessels so that redness appears in the area around the trauma. In addition, a cellular response also occurs marked by the presence of histamine and white blood cells (leukocytes) that migrate to the area around the trauma. If the inflammatory response is successfully reduced, the exudate fluid and proinflammatory cells will slowly disappear so that the tissue is able to regenerate and repair. However, a failed inflammatory response can result in prolonged trauma to the point of becoming chronic (Dermawan *et al*., 2022, p. 76) [15].

Discussion

Oral traumatic ulcer or OTU is a lesion condition in the oral cavity induced by trauma, either chemically, thermally, electrically, or mechanically. This induction is responded to by mucosal cells which cause various changes to occur in the oral mucosal tissue. In OTU conditions, the surface layer of the epithelium is eroded and replaced by fibrin tissue that predominantly contains neutrophils, and there is capillary vasodilation which over time will be replaced by granulation tissue. In addition, inflammatory cells including neutrophils and macrophages travel to the OTU region and infiltrate. This condition lasts for some time until the cause of the trauma is removed. After the trigger for the trauma is eliminated, the wound healing process can take place. Epithelial cell regeneration will begin at the edge of the OTU area, with cells proliferating above the base of the granulation tissue and below the fibrin clot. Cell regeneration continues until the entire OTU area is replaced by new, intact cells (Regezi *et al*., 2021, p.25).

The various stages that accompany the wound healing process can occur faster than the cycle that should occur through the induction of various anti-inflammatory substances, such as flavonoids, phenols, tannins. These three substances are spread in almost all green plants, including petai or Parkia speciosa. The healing of wounds is significantly aided by Parkia speciosa's flavonoid content. In the signalling system that propels wound healing activity, various growth factors, mediators, immune cells, and metabolites control each stage of wound healing.

Wound Healing

Repairing damaged tissue is a complicated and dynamic process that is aided by various cellular processes. Haemostasis, inflammation, proliferation, and remodelling are the four phases of wound healing (Wilkinson and Hardman, 2023, p. 1). Hypertrophic scar tissue and delayed wound healing can result from disruptions in the healing process. Hypertrophic scar tissue is reddish, raised, painful, and itchy. In general, hypertrophic scar tissue due to skin wounds is more common than that due to wounds in the oral mucosa. The reason for this disease is that wounds heal more quickly in the oral mucosa than in the skin (Waasdorp *et al*., 2021, pp. 1-2). Salivary extracellular vesicles contain excessive amounts of tissue factor, which is the cause of this disorder. Chemokines like C-X-C chemokine ligand 4 (CXCL4), C-X-C motif chemokine ligand 5 (CXCL5), and C-X-C motif ligand 8 (CXCL8) are released by activated platelets, fibroblasts, and keratinocytes to draw immune cells to the wound site and quicken the inflammatory phase (Waasdorp *et al*., 2021, p. 8).

Hemostasis

Hemostasis is the body's mechanism to prevent excessive blood loss. A blood clot that closes off a portion of the injured blood vessel is the result of this process, which consists of multiple interconnected elements. The hemostasis process occurs in several stages that take place during the first day (Ozgok & Regan, 2022, p. 1) [39].

Following blood vessel trauma, the first stage starts. Vasoconstriction results from spasms in the blood vessels.

At the location of the damaged endothelium layer, blood components will come into contact with the extracellular matrix (ECM) and collagen. The ECM releases cytokines and pro-inflammatory cells during the second stage, which might lead to platelet adherence and aggregation near the trauma site. Platelet plug development is the result of this mechanism. Glycoprotein receptors, tyrosine kinase receptors, other G-protein receptors, von Willebrand Factor (vWF), and other proteins interact to mediate the haemostasis process of platelet adhesion. Gp 1b-9 in platelets is where von Willebrand Factor binds to function (LaPelusa & Dave, 2023, p.1) [32].

Platelets that have been connected are going through very precise alterations throughout the third stage of the haemostasis process. ADP, serotonin, thromboxane A2, and other activation factors are released into the cytoplasm by platelets. These factors transform into pseudopodal forms which cause a release reaction from various chemokines. The fourth stage is platelet aggregation through the mechanism of various platelets that will be activated. The development of a primary platelet plug will be impacted by these platelets adhering to one another with harmed vascular surfaces (LaPelusa & Dave, 2023, p.1) [32].

The extrinsic route haemostasis process is the fifth step. Tissue factors bind and activate factor VII in this route. The activated factor VII (factor VIIa) will activate factors X and IX by proteolysis. Activated factor IX (factor IXa) will form a bond with its cofactor, namely activated factor VIII (factor VIIIa). This bond leads to the activation of factor X (factor Xa). Factor Xa will form a bond with active factor V (factor Va) and calcium so that it can produce a prothrombinase complex. This complex breaks down prothrombin into thrombin.

The hemostasis process in the intrinsic pathway occurs through the production of thrombin. This pathway transforms factor XI into factor XIa, or active factor XI. Factor IX will become activated factor IX (factor IXa) when factor XIa and activated factor VII are combined. Active factor VIII (factor VIIIa) will combine with active factor IX. Factor X will be activated by this connection. Prothrombin is changed into thrombin via the binding of active factor X (factor Xa) to active factor V (factor Va). In the haemostasis process, thrombin acts as a cofactor and raises the bioactivity of the proteolytic pathway (Waasdorp *et al*., 2021, p. 8).

The development of a fibrin clot is the last step in the haemostasis process. Fibrinogen is changed into fibrin monomers as part of the coagulation cascade. An interconnected fibrin clot is produced when fibrin monomers polymerise to create a fibrin polymer network. Activated factor XIII (factor XIIIa) catalyses this route by stimulating the side chains of lysine and glutamic acid, which causes fibrin molecules to cross-link and form a stable clot (LaPelusa & Dave, 2023, p.1) [32].

Inflammation

Since open wounds give pathogens the perfect environment to colonise, form biofilms, and produce virulence factors, inflammation serves as the primary defence mechanism against pathogen invasion in wounds. Leukocytes entering the trauma site is a hallmark of the cellular response during the inflammatory stage. This reaction happens very fast and is accompanied by the primary signs of inflammation, such as redness or erythema at the trauma site and swelling or oedema. The cellular response typically develops over the first 24 hours and can last for up to 48 hours. Furthermore, immune cells such mastocytes, gamma-delta cells, and Langerhans cells are rapidly activated in the tissue. Traumatised tissue releases inflammation, a localised tissue response. Traumatised tissue releases inflammation, a localised tissue response. Reactive oxygen species, lysosomal enzyme release, and wound healing are all significantly influenced by proinflammatory cells (Gonzalez *et al*., 2021, p. 615).

Damage-Associated Molecular Patterns (DAMPs), which are released by necrotic cells and damaged tissues, and Pathogen-Associated Molecular Patterns (PAMPs), which are released by bacterial components, are the signals that trigger the body's immunological response. DAMPs and PAMPs cause resident cells, which are early indicators of the inflammatory phase, to produce a series of cytokines and chemokines by activating toll-like receptor signals, Receptor for Advanced Glycation End Products (RAGE), and inflammasomes. The resident cells in question include mast cells, Langerhans cells, T cells, and macrophages, neutrophils, and monocytes. Neutrophils are the initial immune cells that reach the wound site and use phagocytosis and degranulation to help combat microbial invasion. Neutrophil cell infiltration peaks three days after tissue damage in oral mucosal tissue damage, while in skin tissue it peaks six days after tissue damage. Additionally, neutrophils release chemokines such macrophage inflammatory protein-1α (MIP-1α) and monocyte chemoattractant protein-1 (MCP-1), to attract monocytes to the wound area. In the tissue, monocytes mature into macrophages that assist the task of neutrophils. An increase in the number of macrophages occurs on the second to fourth day after tissue damage. Macrophages regulate the healing response by secreting cytokines and growth factors that are initially proinflammatory (M1 phenotype) and eventually more anti-

inflammatory and profibrotic (M2 phenotype) during the fin al stages of wound healing, macrophages control the healing response (Waasdorp *et al*., 2021, pp. 8-10; Wilkinson and Hardman, 2023, pp. 2-3).

Several hours after trauma, numerous neutrophils move through the blood capillary walls' endothelial cells. Proinflammatory cytokines including IL-1β, TNF-α (tumour necrosis factor alpha), and IFN-γ (interferon gamma) stimulate endothelial cells at the site of damage. Selectins and integrins, which are already found on the surface of endothelial cell membranes, are among the several adhesion molecules that are determinants of neutrophil diapedesis and are stimulated by these cytokines. Numerous additional facets of tissue repair, including fibrin resolution and extracellular matrix coagulation, angiogenesis stimulation, and reepithelialization, are also influenced by referent cells (Gonzalez *et al*., 20216, p. 615) [22].

Monocyte migration from the blood arteries to the trauma site intensifies 48 hours after the trauma begins. Then, this process produces a new gene expression profile, namely macrophages. Macrophages activated by chemokine signals can act as cells that help neutrophils in phagocytosis. Based on the gene expression profile, macrophages can be classified as activated through the classical pathway (M1 pro-inflammatory) and activated through the alternative pathway (M2 anti-inflammatory and pro-angiogenic). Creation factors like VEGF and PDGF, which are released

by macrophages, are necessary to initiate and promote the creation of new tissue in the injured area. In the tissue repair process, these cells play a crucial part in the change from the exsudative to the proliferative stage (Gonzalez *et al*., 2016, p. 615) [22].

In addition to producing cytokines, pro-angiogenic inflammatory factors, fibrogenic, and free radicals, macrophages also phagocytose detritus. Moreover, macrophages will draw additional inflammatory cells to the damage site after releasing chemotactic proteins. Furthermore, prostaglandins, which are potent vasodilators that alter the permeability of microblood vessels, are also produced by macrophages. The primary cytokines that can promote the development of granulation tissue are PDGF, TGF beta, FGF, and VEGF, which are produced by endothelial cells when these factors combine to activate them (Gonzalez *et al*., 20216, p. 615) [22].

Proliferation

Endothelial cells, fibroblasts, keratinocytes, and epithelial cells move to the wound bed to rebuild the tissue a few hours to days following tissue damage. Endothelial cells and fibroblasts provide structural and nutritional support through the formation of loose and highly vascular granulation tissue. Furthermore, the wound bed is re-epithelialized by keratinocytes and epithelial cells (Waasdorp *et al*., 2021, p. 11; Wilkinson and Hardman, 2023, pp. 3-4).

Hypoxia and an angiogenic reaction are brought on by blood flow in the remaining wound region. The growth of blood vessels brought on by angiogenesis influences the development of hypertrophic scar tissue. Proangiogenic factors, including vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1α (HIF-1α), are released by cells in the hypoxic wound bed. These factors promote endothelial cell migration and proliferation and supply granulation tissue nutrients and immune cells in blood vessel leaks. When compared to the high VEGF content in saliva, the VEGF content in blood vessels is higher. VEGF can prevent endothelial cell apoptosis by increasing antiapoptotic proteins, such as B-Cell Lymphoma (BCL-2). Skin wounds show higher HIF-1α and VEGF content when compared to wounds in the oral mucosa. This condition causes the angiogenesis process in the skin to be greater than in the oral mucosa (Waasdorp *et al*., 2021, p. 11; Wilkinson and Hardman, 2023, p. 4).

To prevent infection, wound tissue can restore its barrier function through re-epithelialization. The re-epithelialization process is influenced by keratinocyte migration and proliferation. Hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF), which are both produced by fibroblasts in the oral cavity, promote keratinocyte migration and proliferation. In addition, integrin proteins that cause keratinocytes to interact with structural proteins are broken down by matrix metalloproteinases (MMPs), such as matrix metalloproteinases-1 (MMPs-1) and matrix metalloproteinases-9 (MMPs-9) so that keratinocyte migration can occur. In addition, saliva containing thousands of proteins and bioactive peptides can stimulate re-epithelialization. Commensal microbes in mouth cavity, like Streptococcus mitis and Streptococcus oralis help accelerate wound closure, while Porphyromonas gingivalis inhibits wound closure (Waasdorp *et al*., 2021, pp. 11-12; Wilkinson and Hardman, 2023, p. 4).

In addition to the restoration of the epithelial barrier, the injured dermis also occurs through the formation of granulation tissue. In order to form a thick fibrillar network that permits cell migration to the wound bed, fibroblasts produce MMPs, which break down the temporary matrix and replace it with granulation tissue containing fibronectin. The increase in fibronectin peaks on the seventh to fourteenth day after tissue damage. Fibronectin in the wound area will form type II collagen as the main type of collagen produced and type I collagen to increase tissue strength and elasticity. The extracellular matrix, which includes matrix-cellular proteins, in addition to fibronectin, initiates the matrix's contact with cells and controls cellular reactions like adhesion, migration, and cell division. Numerous growth factors, including fibroblast growth factor-2 (FGF2), basic fibroblast growth factor (bFGF), and epidermal growth factor (EGF), can promote the migration and multiplication of fibroblast cells. There is no discernible biological impact of salivary FGF2 levels on fibroblast migration. Other salivary peptides, such histatin 1 and histatin 2, exhibit these physiologic effects, though. Immune cells including T cells and macrophages secrete transforming growth factor β (TGF-β), which also affects fibroblast proliferation. The production of scars is linked to transforming growth factor β-1 (TGF-β1), whereas foetal wound healing without scarring is linked to transforming growth factor β-3 (TGF-β3) (Waasdorp *et al*., 2021, pp. 12-13; Wilkinson and Hardman, 2023, p. 4).

Remodelling

After the re-epithelialization process is complete, inflammation is controlled by anti-inflammatory cytokines. The role of pro-inflammatory M1 phenotype macrophages is replaced by anti-inflammatory M2 phenotypes and secrete matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) thus triggering extracellular matrix remodeling mediated by myofibroblasts. Myofibroblast contraction is facilitated by pseudopodial extension which causes cytoplasmic actin to bind to fibronectin in the matrix framework. Myofibroblasts attach to each other via desmosomes and bind to matrix fibers and pull the matrix together which is called contraction. This phase can occur for several weeks to several months. Type I and type III collagen are involved in remodelling, which has an impact on the final quality of scar tissue. Collagen rearrangement or collagen reorganization can cause blood vessel degradation and help wound healing. In addition, the wound will contract so that it reduces the size of the wound and prevents further infection. On the other hand, contraction of the wound may result in diminished tensile strength, stiffer scar tissue, and restricted mobility. When fibroblasts, endothelial cells, and macrophages die or leave the wound site and leave behind scar tissue, the wound healing response is diminished (Waasdorp *et al*., 2021, pp. 13-14; Wilkinson and Hardman, 2023, pp. 4-5).

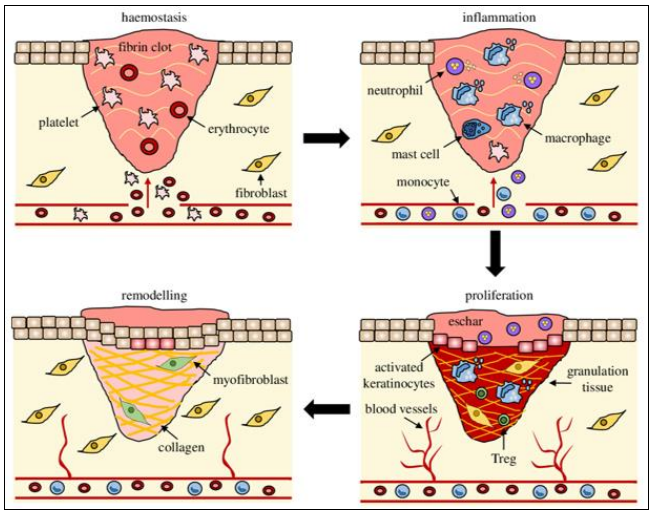

Fig 5: Wound healing phase (Wilkinson & Hardman, 2020, p. 2) [71]

Management of Oral Traumatic Ulcer

Before choosing the right management, identification related to the main etiology of the occurrence of oral traumatic ulcers is carried out. This identification is carried out with the aim of eliminating the main cause of oral traumatic ulcers. Furthermore, management of oral traumatic ulcers can be carried out. If within two to three weeks the oral traumatic ulcer does not improve, an incisional biopsy is recommended so that a histopathological diagnosis can be carried out to observe the condition of the oral traumatic ulcer towards malignancy or not. In addition, the administration of topical anesthesia and the administration of emollients can be an option to help relieve the pain felt by the patient.

In addition, secondary infections due to bacteria entering the wound area that may occur can be managed by applying antibacterials to oral traumatic ulcers. Application of topical antiseptics and antibiotics is an option for treating oral traumatic ulcers, one of the forms of which is mouthwash. Usually, antibiotics have antibacterial activity with a narrow spectrum and can cause drug resistance so that the selection of antibacterials with a broad spectrum is necessary. An example of a preparation that has both antibiotic and antiseptic effects is chlorhexidine. Chlorhexidine is able to destroy dental plaque and has antibacterial properties for twelve hours. However, this antibiotic also causes a burning sensation on the tongue, taste disturbances, changes the color of the teeth, and causes irritation to the esophageal mucosa if swallowed. However, it should be noted that prolonged use of mouthwash containing antibiotics or antiseptics can cause an imbalance in the oral microbiota.

In addition to antiseptic or antibacterial treatment, Liang *et al*. (2024) stated that the strategy for treating oral traumatic ulcers can be done by accelerating wound healing using growth factors (GF). Human epidermal growth factor (HEGF) and hepatocyte growth factor (HGF) have become the treatment options for oral traumatic ulcers. However, GF has a disadvantage, namely that it is easily inactivated.

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