THE EFFECTIVENESS OF CONCENTRATED GROWTH FACTOR AND LOW LEVEL LASER THERAPY ON THE HEALING OF DRY SOCKET

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by

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To my beloved father, who is my pride. To my mother, for her ongoing love and care. To my children who are my motivation and priceless blessings from Allah Almighty. To my sister and my brother for all our beautiful memories and shared dreams. To my husband, for his affection. He and our adorable children beautify our lives. I express my sincere gratitude and appreciation to my supervisor Prof. Dato Dr. Rani Samsudin, Prof. Noor Hayati and Dr. Marzuki Omar for their guidance, patience and encouragement throughout thedevelopment of the project. I would also like to pay special gratitude and many thanks toProf. Rani Samsudin for his unparalleled devotion to knowledge, valuable advice and sincere encouragement.

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LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
cAMP	Cyclic adenosine monophosphate
CGF	Concentrated growth factors
CTGF	Connective tissue growth factor
EGF	Epidermal growth factor
EGFR-I	Epidermal growth factor receptor inhibitor
Er:YAG	Erbium-doped yttrium aluminium garnet laser
FDP	Fibrin degradation products
FGF	Fibroblast growth factor
GT	Granulation tissue
IGF	Insulin-like growth factor
IL	Interleukin
ILGF	Insulin like growth factor
KGF	Keratinocyte growth factor
LED	Light-emitting diode
LIPUS	Low intensity pulsed ultrasound
ND: YAG	Neodymium-doped yttrium aluminum garnet
PBM	Photobiomodulation
PDAF	Platelet-derived angiogenesis factor
PDGF	Platelet-derived growth factor
PF	Platelet factor
PPP	Platelet poor plasma
PRF	Platelet rich fibrin
PRP	Platelet-rich plasma
RBC	Red blood cells
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
t-PA	Tissue-type plasminogen activator
UDHS	University Dental Hospital Sharjah
VEGF	Vascular endothelial growth factor
ZOE	Zinc oxide eugenol

LIST OF APPENDICES

KEBERKESANAN FAKTOR PERTUMBUHAN PEKAT DAN TERAPI LASER TAHAP RENDAH PADA PENYEMBUHAN SOKET KERING

ABSTRAK

Soket kering adalah komplikasi pasca operasi yang biasa berlaku selepas cabutan gigi. Ia berlaku kerana gangguan terhadap pembentukan darah beku di dalam luka. Pelbagai kaedah telah dianjurkan untuk merawat soket kering, seperti penggunaan kunyit, zink oksida eugenol, Alvogyl atau madu. Strategi pengurusan perawatan ini hanya bersifat empirikal untuk menangani gejala dan bukan secara saintifik. Ilmu penyembuhan luka semasa memberi tumpuan kepada strategi selular dan molekul menggunakan alat regeneratif baru. Tujuan kajian ini adalah untuk menilai keberkesanan faktor pertumbuhan pekat (CGF) dan terapi laser tahap rendah (LLLT) dalam penyembuhan soket kering selepas cabutan gigi. Kajian ini dilakukan di University Dental Hospital Sharjah, UAE. 60 pesakit dengan satu soket kering masing-masing, dibahagikan kepada tiga kumpulan rawatan berdasarkan pilihan mereka. Bagi Kumpulan I (n = 30), rawatan konvensional diberikan; soket kering Kumpulan II (n = 15) dirawat dengan CGF, manakala soket Kumpulan III (n = 15) dirawat dengan LLLT. Semua pesakit soket kering dilihat pada hari sifar untuk mendapatkan rawatan dan susulan pada hari ke-4, 7, 14 dan 21. Skor kesakitan, keradangan peri-soket, kerengsaan peri-soket dan jumlah pembentukan tisu granulasi diperhatikan. Data dianalisis sebagai nilai parameter penyembuhan luka purata untuk setiap kelompok perawatan menggunakan ANOVA Sehala. Perbezaan signifikan secara statistik ditetapkan pada $p < 0.05$. Kumpulan Rawatan Konvensional I mengambil masa lebih dari 7 hari untuk menyamai fasa penyembuhan soket dalam Kumpulan II yang dirawat menggunakan CGF dan Kumpulan III yang menggunakan LLLT ($p = 0.001$).

Apabila kadar penyembuhan antara CGF dan LLLT dibandingkan, LLLT Group III menunjukkan kelewatan 4 hari berbanding CGF. Soket yang dirawat dengan CGF lebih baik daripada LLLT dalam kemampuannya menghasilkan 75% tisu granulasi dan menghilangkan gejala kesakitan pada hari ke-7 ($p = 0,001$).

THE EFFECTIVENESS OF CONCENTRATED GROWTH FACTOR AND LOW LEVEL LASER THERAPY ON THE HEALING OF DRY SOCKET

ABSTRACT

A dry socket is a common postoperative complication following tooth extraction. It occurs due to disruption of the clot within the wound. Different methods have been advocated to treat dry socket, such as the application of turmeric, zinc oxide eugenol, Alvogyl or honey. These management strategies have been empirical for treatment of symptoms only rather than scientific. Current wound healing sciences focuses on the cellular and molecular strategies using new regenerative tools. The aim of this study is to evaluate the efficacy of concentrated growth factor (CGF) and low level laser therapy (LLLT) in the healing of dry socket following tooth extraction. The study was conducted at University Dental Hospital Sharjah, UAE. 60 patients with one dry socket each, were divided into three treatment groups based on their choice. In Group I (n=30), conventional treatment, Group II (n=15) dry sockets were treated with CGF and Group III (n=15) sockets were lased with LLLT. All dry socket patients were seen at day 0 for treatment and followed up at day 4, 7, 14 and 21. Pain score, peri-socket inflammation, peri-socket tenderness and amount of granulation tissue formation were noted. Data were analyzed as mean wound healing parameter values for each treatment group using One-way ANOVA. Statistically significant difference is kept at $p<0.05$. Conventional Treatment Group I took more than 7 days to match the healing phase of Group II CGF treated socket and Group III LLLT irradiated socket ($p=0.001$). When healing rate between CGF and LLLT are compared, LLLT Group III showed a delay of 4 days compared to CGF. CGF treated socket was superior to LLLT in its ability to generate 75% granulation tissue and eliminate pain symptom by day 7 ($p=0.001$).

CHAPTER 1

INTRODUCTION

1.1 Background

Oral wounds are inflicted daily following oral surgery practice. Tooth extraction is a very common oral surgery practice and heal naturally unless disturbed by intruding factors (S. A. Hamad, J. S. Naif, & M. A. Abdullah, 2016). One of the most common post extraction complication is dry socket (Almutairi 2019) (M. Eshghpour, Ahrari, Najjarkar, & Khajavi, 2015; S. A. Hamad et al., 2016) (Figure 1.1). In dental literature, the terminology 'dry socket' and 'alveolar osteitis' are interchangeable. It commonly occurs from day one to day three post-extraction, and is also characterized by severe pain, halitosis, loss of activity and occasional regional lymphadenitis (Helei 2019; Noroozi 2009). Maximum pain symptoms in dry socket occur at 12 -48 hours post extraction (Majid Eshghpour, Moradi, & Nejat, 2013; S. A. Hamad et al., 2016). This condition occurs when the socket is devoid of blood clot and the healing epithelium (Mamoun, 2018), resulting in the exposure of the alveolar bone (Shehab Ahmed Hamad, Jandar S Naif, & Mahdi A Abdullah, 2016). The leading symptom is pain (Helei, Zhero, Helei, & Kryvanich, 2019; Noroozi & Philbert, 2009; Preetha, 2014) and it is rarely associated with facial swelling or cellulitis.

Dry socket can be defined as ‘post-extraction pain at and around the tooth extraction site, which rises in intensity at any time between the first and fifth day after tooth removal, followed by incomplete or total loss of the blood clot in the socket, with or without halitosis’ (Blum, 2002; Preetha, 2014).

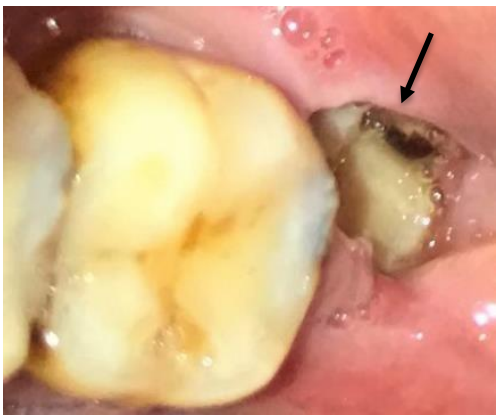

Figure 0.1 Arrow: A classical feature of dry socket following extraction of a mandibular third molar, devoid of blood clot with dry alveolar exposure

Different method have been used to treat this condition such as irrigation with hydrogen peroxide (Rauf, Kamal, & Farooq, 2014) and chlorhexidine (Hita-Iglesias, 2008), honey (Ansari et al. 2019), turmeric (Lone, wakeel Ahmed, Prasad, & Ahmed, 2018), alvogyl (Supe et al. 2018), holisal gel (Zorina, Petrukhina, & Boriskina, 2019), colloidal silver (Helei et al., 2019), hyaluronic acid (Dubovina et al. 2016), clindamycin and rifampicin (Çebi, 2020). The most common approach to treat the dry socket is curettage followed by irrigation with normal saline. This conventional method addresses the symptoms only but does little to promote the healing of the socket.

In today's era there are new treatment options which work at the cellular and molecular level to reduce the symptoms and promote wound healing regenerative process. Such treatment options include the use of platelet rich plasma (PRP) (Prataap, 2017), concentrated growth factor (CGF) (Malli Sureshbabu, Selvarasu, Nandakumar, & Selvam, 2019), low level laser therapy (LLLT) (Parihar & Pathak, 2018), ozone (B. T. Khan et al., 2015) and low-intensity pulsed ultrasound (LIPUS) (Tanaka, Kuroda, Horiuchi, Tabata, & El-Bialy, 2015).

Corigliano was the first to prepare the 'Concentrated Growth Factor' (CGF) in 2010 (Qiao, Duan, Zhang, Chu, & Sun, 2016). It is the third-generation autologous plasma that is extracted from blood by centrifugation (Malli Sureshbabu, Selvarasu, Nandakumar, & Selvam, 2019). It is comprised of essential growth factors that are the regulators of tissue regeneration (Jin et al., 2018).

Endre Mester was the one to discover low level laser therapy (LLLT) based on his observation of hair growth in mice after the application of laser light (Chung et al., 2012). It is fundamentally a photochemical effect that induces cellular stimulation on the skin (S. A. Hamad et al., 2016). Such photostimulatory effect promotes fibroblast proliferation (M. Eshghpour et al., 2015; S. A. Hamad et al., 2016), stimulation of platelet derived growth factor (PDGF) (Kesler, Shvero, Tov, & Romanos, 2011), bone regeneration (S. A. Hamad et al., 2016) and collagen synthesis (Kesler et al., 2011) with minimal thermal damage.

The purpose of this study is to evaluate the effectiveness of concentrated growth factor (CGF) and low level laser therapy (LLLT) in accelerating the healing of the alveolar osteitis.

1.2 Statement of the Problem

Dry socket is a very common wound healing complication following the tooth extraction. It causes severe pain and delay the healing process. Up till today, there is no consensus on the appropriate management of dry socket**.**

1.3 Rationale of Study

There are different approaches to treat dry socket, but they are merely symptomatic treatment aim to alleviate the symptoms, but the main etiology is not addressed. Thus, most treatments do not support the healing of the dry socket. There is a need for a new approach which should be based on the understanding of the molecular aspects of wound healing management.

1.4 General Objective

To investigate the effectiveness of concentrated growth factor (CGF) and low level laser therapy (LLLT) on the healing of dry socket when compared to the conventional treatment.

1.5 Specific Objectives

1. To quantify the formation of granulation tissue in dry sockets using CGF and LLLT.
2. To evaluate the effectiveness of CGF and LLLT in relieving symptoms of dry socket.
3. To evaluate the effectiveness of CGF and LLLT in the overall healing of dry socket compared to conventional technology.

1.6 Research Question

Is there any technique that could stimulate and enhance the regeneration process in dry socket healing?

1.7 Hypothesis

It is possible to accelerate dry socket healing with CGF (concentrated growth factor) or LLLT (low level laser therapy) and relieve its symptoms.

CHAPTER 2

LITERATURE REVIEW

2.1 History of Dry Socket

Dry socket is common following normal tooth extraction and its occurrence is rampant following surgical extractions of mandibular third molar (S. A. Hamad et al., 2016). A growing body of literature is dedicated to alveolar osteitis addressing the etiology and pathophysiology of this condition. It occurs in both healthy and medically compromised individuals (M. Eshghpour et al., 2015; S. A. Hamad et al., 2016).

There has been lots of controversies regarding the best terminology used for dry socket as well as understanding its etiology, pathophysiology and methods of prevention and treatment. The literature is ample with various descriptive definitions for alveolar osteitis, which likely results in the discrepancy in the diagnostic standards. Numerous authors have agreed that pain and empty alveolus are observed in all patients with alveolar osteitis. Different clinical defining factors include radiation of pain in the direction of the ear and temporal area, unusual maxillary involvement in ocular and frontal regions, halitosis, occasional low-grade fever, inflamed gingival margin, exposed bone, ipsilateral regional lymphadenopathy, and grayish discharge

Many authors do not agree on the appropriate terminology for this problem. Crawford was the first one to describe the term 'dry socket' in 1896 (Crawford, 1896; Preetha, 2014).

2.2 Historical Terminology of Dry Socket

The term 'dry socket' describes the dry appearance of the socket after the clot is dislodged and the remains are washed away. Different terminologies are being used for the condition, which includes “alveolar osteitis”, “alveolitis”, “localized osteitis”, “alveolitis sicca dolorosa”, “localized alveolar osteitis”, “fibrinolytic alveolitis”, “septic socket”, “necrotic socket”, and “alveolalgia” (Cardoso, Rodrigues, Ferreira Junior, Garlet, & de Carvalho, 2010; Preetha, 2014). Birn, whose series of articles gave better information on the pathophysiology, categorized the condition as fibrinolytic alveolitis. The terms “Dry socket” and “alveolar osteitis” are commonly used and easily understood terms. Various authors over the years gave different definitions for ‘dry socket’, as shown in Table 2.1.

Infected Socket

An infected socket following tooth extraction is commonly misunderstood for a dry socket. Following tooth extraction, the blood clot gets dislodged resulting bare bone, this is a dry socket. An infected socket occurs by the bacteria infecting the gingiva around the exposed socket from one to two days post extraction, that causes swelling and redness. The significant contributor for an infected socket is the oral hygiene of the patient (Shaifulizan Abdul Rahman et al., 2014).

Table 2.1 Definitions of dry socket throughout history (Blum, 2002*)*. Dry sockethas been defined in many ways over the past 100 years.

Author and Year	Definition
Hermech et al. (unspecified)	Loss of blood clot and/or necrosis of blood clot and persistent or increasing postoperative pain after the surgery, with throbbing pain at the surgical site that isnot relieved with mild analgesics.
Laird et al. (unspecified)	Evidence of breakdown of clot together with the characteristic foul odour.
Ritzal et al. (unspecified)	The simultaneous presence of a severe irradiating pain originating from the emptysocket and the disintegration (partial or total) of the socket coagulum.
Crawford (1896)	Severe, neuralgiform, irradiating pain and partial or total disintegration of the bloodclot in the socket have to be present simultaneously.
Birn (1972)	Partial or complete loss of the blood clot, exaggerated pain radiating to the ear andtemporal region, and a putrid odour.
Vedtofte et al. (1974)	Complete or incomplete loss of the blood clot with exposed bone in the alveolusand extreme irradiating pain.
Sweet & Butler (1977)	Severe pain, foul, greyish exudate, and necrotic odour and debris at the extractionsite.
Rood & Murgatroyd (1979)	A painful socket which is increasing in severity 24 h after the extraction.
Tjernberg (1979)	Disintegrated blood clot in combination with pain that is not adequately relieved byanalgesics.
Davis et al. (1981)	Loss of an adequate clot and development of delayed pain, 2 to 5 days aftersurgery, that was suffice to require active medical intervention.
Meechan et al. (1987)	Pain from extraction site and empty or necrotic entity containing socket.
Sorensen & Preisch (1987)	Return of patient 2 or more days postoperatively complaining of pain in the extraction area and the presence of a denuded socket on clinical examination.
Fridrich & Olson (1990)	Absence of a demonstrable clot and symptomatic pain in or around the surgical site36 h after surgery that was suffice to require active medical intervention.
Larsen (1991)	Persistent or increasing postoperative pain beginning after the second day, which is associated with necrotic tissue in the socket, exposed bone, or loss of the clot onclinical examination.
Akota et al. (1998)	The presence of a disintegrated blood clot, and/or increased pain in the socketregion, and/or foul odour, and/or exudate or pus in the socket.
Bloomer (2000)	Complain of pain in the extraction site and the presence of exposed bone ornecrotic debris.

2.3 Epidemiology of Dry Socket

The dry socket incidence varies from 1% to 4% worldwide (M. Eshghpour et al., 2015). It occurs in 0.5-5% of routine dental extractions and 25-30% in the extraction of impacted mandibular third molars (Bowe, Rogers, & Stassen, 2011; Daly, Sharif, Newton, Jones, & Worthington, 2012; Preetha, 2014). The prevalence of dry socket has been stated to be as high as 35% in a few studies (Nusair & Younis, 2007). Mudali et al. (Mudali & Mahomed, 2016) described that the dry socket is more frequent in the mandible. A report showed that the prevalence of dry socket in mandible is 7 to 10 times higher than in maxilla (Nusair & Younis, 2007) (Figure 2.1).

Interestingly dry sockets were evaluated to be significantly less frequent after multiple extractions than single extractions (MacGregor, 1968). Females are more often affected than males, but rather than any inherent gender predilection, this seems to be due to oral contraceptive use (Wray, Stenhouse, Lee, & Clark, 2003; Xu et al., 2015). The majority of dry sockets occur in individuals aged between 20 and 40 years which is when most dental extractions occur. Patients aged 18 years or older have higher incidence of dry socket as compared to younger patients which are below 18 (Cardoso et al., 2010; Chiapasco, Crescentini, & Romanoni, 1994).

These compromised healing affects both hard and soft tissue regeneration. An understanding of normal wound healing may enlighten us on the ways to negotiate the complexity in managing dry socket.

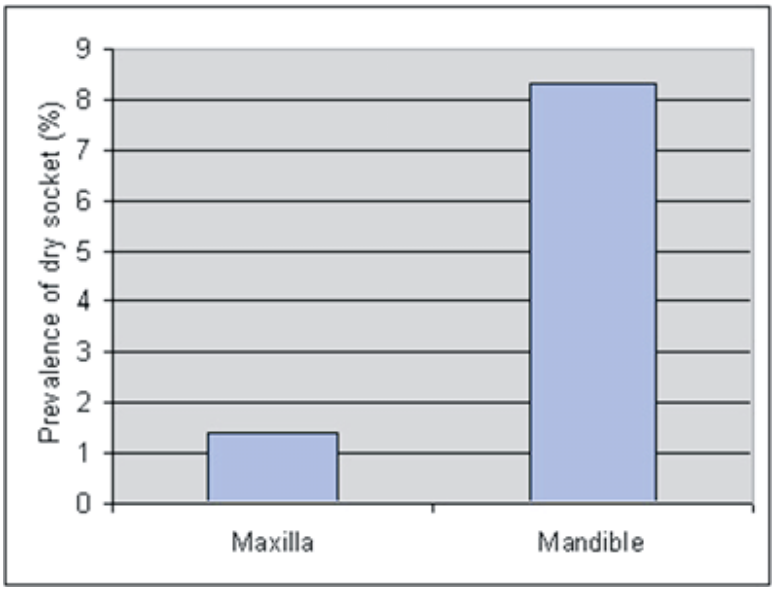

Figure 2.1 Prevalence of dry socket in the maxilla and mandible.
Source: (Nusair & Younis, 2007)

2.4 Blood Supply of Tooth and Periodontium

Blood supply of mandibular teeth are from the arteries that are the derivatives of inferior alveolar artery, on the other hand interdental and interradicular arteries supply the alveolar bone and periodontal ligament (Roush, 1989) (Figure 2.2). The maxillary artery that is the terminal artery from external carotid artery is the source of origin of the inferior alveolar artery (Nguyen, 2019).

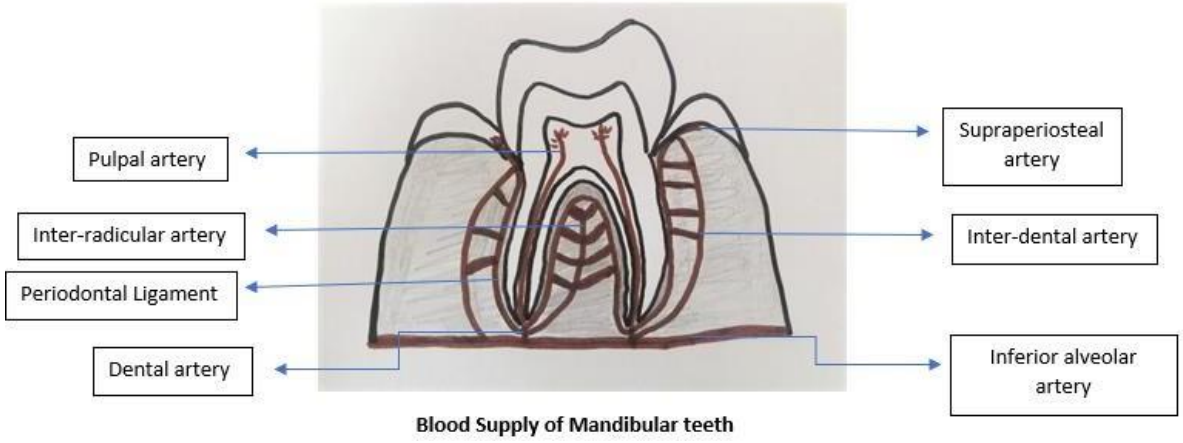

Figure 2.2 Arterial supply of mandibular teeth. These arteries rupture during extraction of a tooth leaving a clot in the socket.

The arterial supply for periodontal ligament is from inferior and superioralveolar artery for mandible and maxilla respectively (Figure 2.3). Each periodontal ligament has three sources of blood supply, namely the apical vessels which supply dental pulp, the intra-alveolar vessels which penetrate the alveolar bone and the gingiva vessels which enters the periodontal ligament coronally (Nan Jiang, Weihua Gup et al. 2015). All these arteries rupture during extraction of the tooth leaving a clotin the socket. This begins the process of socket wound healing.

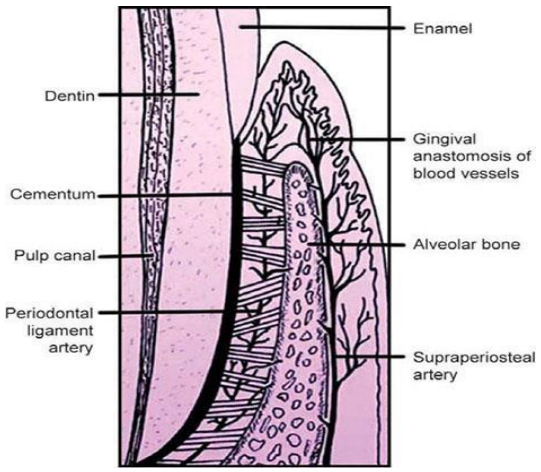

Figure 2.3 Periodontal ligament blood
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2.5 Normal Wound Healing

Normal wound healing is a systematic process, traditionally explained in terms of four overlapping classic phases (Figure 2.4), namely hemostasis, inflammation, proliferation and finally maturation state. Platelets perform a vital part in the formation of clots during hemostasis. Inflammatory cells debride damaged tissue during the inflammatory phase. During proliferative phase, the epithelialisation, fibroplasia, and angiogenesis phase take place. In the meantime, the granulation tissue forms, and the wound starts contracting. Subsequently, in order to produce more tensile strength of scar, the collagen forms close cross connections with other collagen and protein molecules during the maturation stage.

Growth factors play a very important role in the healing of a wound. These growth factors are present in the alpha-granules of platelets such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), platelet factor interleukin (IL), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and insulin-like growth factor IGF (Lubkowska, Dolegowska, & Banfi, 2012). Investigations have shown that the healing process can be accelerated in the presence of growth factors (Lubkowska et al., 2012).

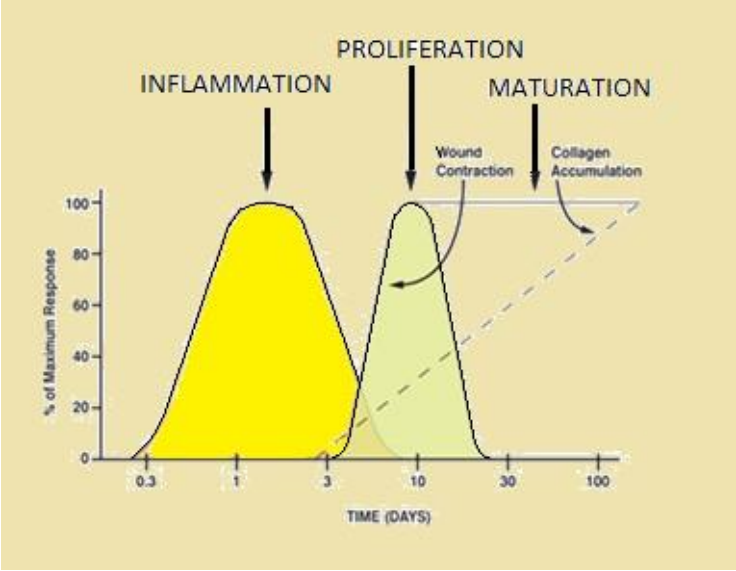

Figure 2.4 Phases of Wound Healing.

2.5.1 Post Extraction Clot Formation

Dry socket occurs when the blood clot is dislodged from the socket after tooth extraction and the bony socket is exposed. In a normal situation, a prothrombin activator converts prothrombin into thrombin. Thrombin, which is an enzyme converts fibrinogen into fibrin, which forms a blood clot forms at the tooth extraction site (Figure 2.5).

The blood coagulation cascade is promoted via complex enzymes comprising a vitamin k dependent serine protease and a co factor protein that is organized on a membrane outside in a calcium-dependent way (Butenas & Mann, 2002). In their pure substrates, these complexes are 10^5-10^9 fold more active in proteolysis than enzymes individually, this information is based on information obtained by using multiple in vitro blood coagulation entities (Butenas & Mann, 2002). Tissue factor-initiated thrombin generation can be divided in two levels: an initiation phase and a propagation phase. The initiation step or phase is described by the formation of nanomolar quantities of thrombin, femto to picomolar quantities of factors VIIa, IXa, Xa, and XIa, partial platelet activation, and almost quantitative activation of pro cofactors V and

VIII. The period of this phase is mostly affected by concentrations of tissue factor and tissue factor pathway inhibitor (TFPI). The characteristic functions of the propagation section are quantitative prothrombin activation at an excessive rate, completion of platelet activation, and solid clot formation. This section is in general regulated via antithrombin III and the protein C system. During the propagation stage, thrombin generation is extremely decreased in the absence of factor VIII and factor IX (hemophilia A and B, respectively) and is also decreased at platelet count less than 5% of mean plasma concentration (Butenas & Mann, 2002).

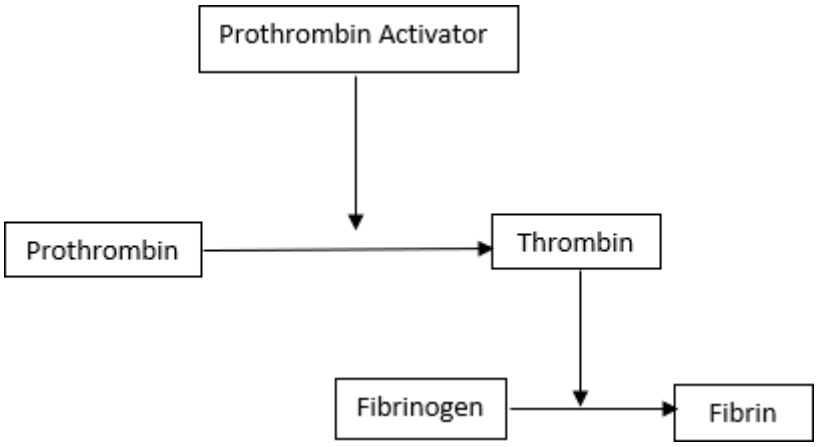

Figure 2.5 Conversion of prothrombin into thrombin. A prothrombin activator converts prothrombin into thrombin. Thrombin which is an enzyme converts fibrinogen into fibrin. Source: Linda Crampton, https://owlcation.com

The clot acts as a protective coating upon the empty bone and the nerve endings in the empty tooth socket. The clot also forms the basis for new bone generation and soft tissue development over it. Dislodgment of this vital clot leads to the formation of the dry socket.

2.5.2 Normal Healing of the Extraction Socket

The known factors for optimal bone healing are vascularization, adequate cells, nutritional elements and required signal stimuli (Khullar et al. 2012). The regularhealing of the extraction socket includes five phases: the granulation stage, the initialangiogenic/neurovascular stage, the new bone formation, the phase of bone growthand the phase of bone reorganization (Khullar et al. 2012).

Granulation stage

This stage lasts from the day of extraction up to five days. At the base of the socket, early granulation tissue is seen, this then stretches along the socket wall. (Figure 2.6). A blood clot forms first at the central part of the socket. Early angiogenesis happens at this stage, the sprouting or budding extensions of existing blood vessels sinusoidal capillaries that is formed from the blood vessel endsin the residue of the periodontal ligament at the cribriform plate. This all begins at thebase of the socket. This is the least injured area during tooth extraction. The vascular pattern remains intact in this area.

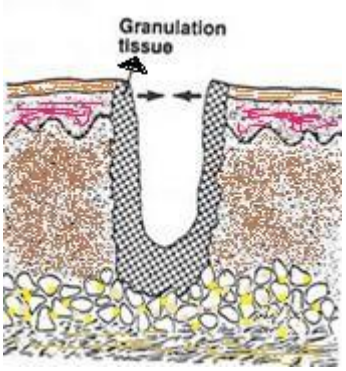

Figure 2.6 Schematic drawing of laying of granulation tissue in a healing lower tooth socket. Granulation tissue formation generally begins at the base of such socket because of its proximity to the main blood supply of the socket and the apex of the socket is usually the least traumatic site during non-surgical extraction.

Initial angiogenic / neurovascularization stage

This stage goes up to one week after tooth extraction. Blood clot decrease in size. The formation of new sinusoids along the socket wall makes the base shift above the height of the clot until the newly formed sinusoids fills about the two third of the socket. The first new bone trabeculae may be observed.

New bone formation stage

This happens after about two weeks from the day of extraction. The freshly developed sinusoids fill the entire socket with granulation tissue. With a lattice of trabeculae, bony walls at the base as well as at the side of the socket become thick. There is a relationship between immature sinusoids and new bone. Incompletely ossified trabeculae delineate the woven bone. Bone development becomes rapid.

Bone growth stage

This stage begins at four to five weeks. More trabeculae are accumulated at the base as well as the walls of the socket.

This how, socket has two third of the original volume of the socket. The secondary spongiosa of the next phasestarts to buildup.

Bone reorganization stage

This stage begins at the sixth week after extraction. Primary spongiosa rearranges into an irregular as well as larger structure just as secondary spongiosa. It commences at the base of socket and extends upwards.

2.6 Aetiology of Dry Socket

Uptil now, there is no evidence for exact aetiology of dry socket. The foremost school of concept concerning the aetiology of a dry socket taking place following a tooth extraction is based on the idea that a blood clot fails to form (DW Nitzan, 1983).

However, the clot is then lysed, that brings on the intense signs and symptoms of a dry socket. The dry socket development is most efficiently explained by fibrinolysis induced by tissue activators. Based on the literature records, it is suggested that fibrinolysis involves bacterial agents and that Treponema denticola could additionally play as the main component in this condition (DW Nitzan, 1983).

Fibrinolysis is a process which removes fibrin deposits by the enzymatic action of the fibrin meshwork into smaller soluble components (Buller & Sweet, 1977). Fibrinolytic activity heightens in dry sockets together with activation of plasminogen to plasmin in the presence of tissue activators (Herluf Birn, 1973; Serrati et al., 2006). Increase in fibrinolysis decreased the chance of dissolution of the blood clot before the second day after extraction because the clot contains antiplasmin, which must be neutralized before clot dissolution can occur (H Birn, 1970). Fibrin is an insoluble protein that is formed in response to bleeding and it composes the major component

of a blood clot. Fibrin is a strong protein material organized in long fibrous chains; it is derived from fibrinogen, a soluble protein that is produced in the liver. When tissue damage leads to bleeding, the fibrinogen transforms into fibrin at the wound site, by the action of thrombin which is a clotting enzyme.

Fibrin molecules then combine to form long fibrin threads which entangles platelets, building up a spongy mass that gradually hardens and contracts to form the blood clot. A material known as a fibrin-stabilizing factor or factor XIII stabilizes this hardening process. Plasmin like activity in dry sockets is not present at normal extraction sites (H Birn, 1972a; Cardoso et al., 2010; Serrati et al., 2006). Kinases are liberated during inflammation through direct or indirect activation of plasminogen in the blood. These kinases cause lysis and destruction of the blood clot (Preetha, 2014; Serrati et al., 2006).

An increased fibrinolytic activity has been identified as a major factor in the pathology of the dry socket (H Birn, 1972a; Cardoso et al., 2010; Serrati et al., 2006). A single chain of glycoprotein with 791 amino acid residues and 2% carbohydrate is a normal human plasminogen. The precursor of plasmin is the plasminogen type I, that is a potent serine protease and it is involved in the breakdown of fibrin clots.

This plasminogen is released after routine tooth extraction (Figure 2.7 and 2.8). Plasminogen type-1 tends to be more readily recruited into blood clots. The principal endogenous plasminogen activator in the blood is the tissue-type plasminogen activator (t-PA). It is produced by vascular endothelial cells as a single-chain molecule and is secreted into the plasma by an acute release after stimulation of certain endothelial cell receptors, such as in the injury of tooth extraction. It is also known that thrombosis can be caused by plasmin deficiency, as clots are not adequately degraded.

The activity of plasmin is halted mainly by binding to a plasmin inhibitor, that forms a stable plasmin compound devoid of proteolytic activity. Thus, increase in plasmin causes fibrinolysis, increasing fibrin degradation product which results in condition like dry socket (Figure 2.7) (Cardoso et al., 2010; Serrati et al., 2006). Other factors such as tumor necrosis factor, interleukin-1 and inflammatory cytokines are known to interfere in the process of healing (Cardoso et al., 2010; Serrati et al., 2006).

Irregular regulation in cytokines or growth factors drastically change the typical wound healing phenomena as well as block the improper formation of particular pro-inflammatory cytokines or supplement with more amounts of growth factors, the key role is performed by these mediators. Protein-based and DNA-based (gene transfer) therapies are undergoing clinical progress as an effective tool for improving healing processes (Efron & Moldawer, 2004). Following trauma, direct activators are released into the alveolar bone cells. Bacteria release indirect activators (Daly et al., 2012; Kolokythas, Olech, & Miloro, 2010). Tissue plasminogen activators and endothelial plasminogen activators are direct extrinsic activators. Direct intrinsic activators include plasma elements like factor XII, urokinase. Kinin produces intense pain in concentration as small as 1mg /ml (Barrientos, Stojadinovic, Golinko, Brem, & Tomic-Canic, 2008; H Birn, 1972b).

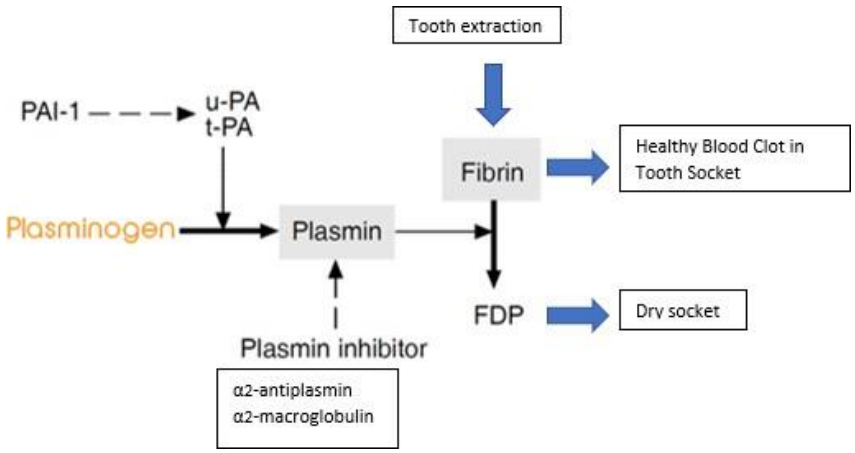

Figure 2.7 Molecular Process of Dry Socket
The precursor of plasmin that functions in the degradation of fibrin is plasminogen type-1. The plasmin inhibitor protects the active plasmin site sterically, thus significantly reducing the access of plasmin to protein substrates.
t-PA: tissue-type plasminogen activator; FDP: fibrin degradation products.
https://diapharma.com/plasminogen-plg/

2.7 Risk Factors for Dry Socket

Various systemic as well as local factors play role as a risk factor for dry socket (Blum, 2002; Cardoso et al., 2010; Vezeau, 2000) such as periodontal disease, acute necrotizing ulcerative gingivitis, local bone disease, paget's disease of bone, osteopetrosis, cemento-osseous dysplasia, a history of previously developing a dry socket with past extractions and inadequate oral hygiene (Daly et al., 2012; Odell,2010; Preetha, 2014). Postoperative factors that may lead to loss of the blood clot include forceful spitting, sucking through a straw, and coughing or sneezing (Daly et al., 2012).

Excessive local trauma and bacterial invasion are also one of the factors. Pyrogens that are released by bacteria can be an indirect activators of fibrinolysis in vivo, which is also a major factor (Cardoso et al., 2010; J. Catellani, 1979). Trauma

also affects wound healing in a dry socket. Aggressive curettage also has serious effects on dry socket wound healing. There could be probably 21.9% incidence of dry socket in therapeutic (presence of infection and caries) compared to 7.1% in prophylactic (without any symptoms) extractions (al-Khateeb, el-Marsafi, & Butler, 1991; Cardoso et al., 2010). In the socket, dental and osseous remains were also considered a possible cause of dry socket (Herluf Birn, 1973; Cardoso et al., 2010; Simpson, 1969).

Poor oral hygiene and alveolar contamination affects healing in dry socket as well (Cardoso et al., 2010; Penarrocha, Sanchis, Saez, Gay, & Bagan, 2001; Rud, 1970). Oral contraceptives might also affect wound healing in dry socket (Cardoso et al., 2010; Cohen & Simecek, 1995; Garcia, Grana, Sampedro, Diago, & Rey, 2003). Smoking and alcohol affect wound healing seriously (Cardoso et al., 2010; Monaco, Staffolani, Gatto, & Checchi, 1999; Sweet & Butler, 1979). Nicotine, cotinine, carbon monoxide, among others, are cytotoxins for several types of cells and consequently inhibit the healing process (Cardoso et al., 2010; Cryer, Haymond, Santiago, & Shah, 1976; Grossi et al., 1997; Lawrence, Murphy, Robson, & Heggers, 1984; Silverstein, 1992).

There is a relation between dry socket and diabetes (Karbassi et al., 2015). There are more chances of the occurrence of complication like alveolar osteitis in diabetic patients than non- diabetic patients (Karbassi et al., 2015). The use of oral contraceptives causes higher risk of dry socket (Kanwal, Muttappallymyalil, Al-Sharbatti, & Ismail, 2017; Xu et al., 2015). The dentist should cautiously approach for tooth extraction for patients taking oral contraceptives (Xu et al., 2015).

The age of a person affects the occurrence of dry socket (B. T. Khan, Kiani, Saeed, & Khan, 2015). Age has surprisingly an inverse relation with the risk of dry

socket (B. T. Khan et al., 2015). It is suggested that the formation of dry socket is more among females (Upadhyaya & Humagain, 2010).

Trauma and difficult surgical procedure is thought to be related to the formation of the dry socket (Herluf Birn, 1973; Colby, 1997; Rakhshan, 2018). More trauma has been known to bring about delayed wound recovery (Rakhshan, 2018). A reduction in blood perfusion is because of compression of the alveolar bone. The trauma may cause thrombosis in the underlying vessels (Blum, 2002). The harm to the alveolar bone cells causes inflammation, liberating tissue activators of fibrinolytic activity into the alveolus, therefore, inflicting dry socket (Herluf Birn, 1973; Rakhshan, 2018).

The tooth and bone fragments mixed with different debris can cause prolong wound healing (Blum, 2002).

Role of bacteria in the formation of alveolar osteitis has long been a theory (Rood & Murgatroyd, 1979). This concept was supported by much work in this field. Many cases of dry socket or alveolar osteitis were seen in patients with poor oral hygiene, pericoronitis and periodontal diseases (Penarrocha et al., 2001; Rud, 1970). This concept was further supported by the evidence of reduced alveolar osteitis in conjunction with antimicrobial therapy (Chapnick & Diamond, 1992; Swanson, 1989). There were many efforts done to isolate the causative micro-organism. After much efforts, two micro-organisms were brought into notice, which were ‘actinomyces viscous and streptococcus mutans’ (Rozanis, Schofield, & Warren, 1977). These micro-organisms were inoculated in animal models and so delayed wound healing was observed after extraction. Similarly, a significant role of anaerobes in pericoronitis becomes more clear (D Nitzan, Sperry, & Wilkins, 1978).

2.8 Clinical Features

Dry Socket occur in both healthy and medically compromised individuals (M. Eshghpour et al., 2015; S. A. Hamad et al., 2016). Dry socket is associated with intense pain and the symptoms reaches its maximum intensity at 12 -48 hours after surgery (S. A. Hamad et al., 2016). The socket is devoid of blood clot (Mamoun, 2018), resulting in the exposure of the bare alveolar bone. Dry socket commonly occurs from day one to day three post-extraction and is also characterized by halitosis and occasionally regional lymphadenitis (Helei et al., 2019).

The common clinical features of alveolar osteitis are:

- Pain at extraction site
- Facial swelling or lymph node swelling
- Partial or complete loss of the blood clot that is notice as an empty-looking (dry) socket.
- Presence of visible bone in the socket
- Radiation of pain from the socket to eye, ear, neck or temple on the same side as the extraction.

Dental radiograph excludes the conditions which can be misdiagnosed as dry socket such as retained broken down roots, bony pieces and fracture of the alveolus, body of the mandible.

Pain is the key symptom is dry socket. The prime differentiation between regular post extraction pain and dry socket pain is the timing characteristics. Post-extraction pain rises and dissipates for 24 hours, but the pain rises for two to five days after extraction in dry socket condition and needs professional attention.

The web of vessels in the socket wall is the source of the granulation tissue accountable for healing.

The exposure of the bone and nerves causes severe pain not just in the socket but also along the nerves which radiate to the side of the face. The socket gets inflamed and might fill with the food particles, elevating the pain.

The dry socket leaves underlying nerves uncovered, which could be very painful. The condition needs to be treated by a professional who cleans the site and may place a unique dressing into the socket.

Drugs like ibuprofen or antibiotic can be used to deal with the pain and to decrease swelling.

2.9 Prevention of Dry Socket

It is quite tricky for a clinician to advocate the preventive measures for dry socket because we do not understand its actual etiology. However, there are general measures which the practitioner or the patient can take to prevent its occurrence.

There is a significant role of antibiotics in the prevention of alveolar osteitis both in systemic and topical form (Ramos, Santamaria, Santamaria, Barbier, & Arteagoitia, 2016). Its antibacterial effects lower the bacterial invasion and risk of infection (Noroozi & Philbert, 2009). Avoiding tobacco is very important for the prevention of dry socket.

2.10 Management of Dry Socket

Dry socket is commonly managed using the conventional method in which the site is rinsed with normal saline irrigation, followed by curettage of socket and placement of a dressing material which such as zinc oxide eugenol (ZOE) or alvogyl. This whole procedure is done under local anesthesia. Other than normal saline various