

*PENTO Protocol and Oral Wound Healing: A Case Report***Yousry Nagib Eldek**

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Abstract

Extraction of the teeth is the most common procedure carried out in the denal clinic. The healing process is uneventful following dental extraction in most cases. However, the healing process may be disturbed even in normal healthy patients for different causes in some cases . Pentoxifylline (PTX) and Tocopherol have beneficial effects to to improves wound healing. A 48-year-old female patient received simple dental extraction to her tooth and suffered from delayed healing of the extraction socket. Combination therapy of Pentoxifylline and Tocopherol was prescribed to improve the healing. The result of the presented case revealed that PENTO protocol was useful for delayed wound healing cases.

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Case Presentation

A 48-year-old female patient presented to the dental department complaining of pain related to the remaining roots of right upper first molar. The medical history reported that she is taking contraceptive pills. She received Hyaluronic acid injection 3 months ago to treat her knees pain and osteoarthritis. She was suffering from hypothyroidism and she was taking 25 mcg Thyroxine for 6 months, and then she stopped it according to the medical instructions after repeating the investigations 4 years ago. Recent investigations

revealed normal level of TSH and Hb A1C and low level vit D 25-OH (33.2 nmol/L). The extraction was performed easily. Paracetamol tablets (1 gm 2 hours postoperatively, and then 1 gm every 8 hours) were prescribed. Postextraction instructions were given. The patient came after 1 week complaining of continuous, severe, and deep-seated pain in and around the extraction site which mildly relieved by Paracetamol. On examination, there was profound erythematous inflamed mucosal tissue and the socket was empty and the bone was exposed , while there was

no blood clot or suppuration. The treatment included irrigation of the socket using warm normal saline in addition to pain medication (Ibuprofen tablets 400 mg) every 12 hours for 5 days and oral administration of Amoxycillin capsules (500 mg every 8 hours daily for 5 days) and Metronidazole tablets (500 mg every 8 hours daily for 5 days). The patient was advised to return after 3 days for follow up, but she returned after a week with the same problem (Fig.1). New treatment protocol was prescribed to improve the process of the healing and included a therapeutic regimen with PENTO protocol (Pentoxifylline 400 mg BID and Tocopherol 400 IU BID) for managing delayed healing of extraction socket with clinical evaluation every week (Fig. 2). PENTO protocol showed noteworthy results in managing the socket healing after 1 month (Fig.3). She also felt coincidental improvement in her knees and pain relief.



Figure 1: socket extraction after 2 weeks



Figure 2: socket extraction after 4 weeks



Figure 3: socket extraction after 6 weeks

Discussion

Following tooth extraction, the socket will be filled with a blood clot, which will be replaced by granulation tissue and followed by epithelialization over 7 days. Tissue organization develops to complete epithelialization in a few weeks. Therefore, delayed wound healing is considered as any area of bone exposure in the extraction socket because of less epithelialization that could be visually confirmed more than 10 days after tooth extraction[1].

The healing process of the socket occurs through 4 stages which includes : hemostasis, inflammation, proliferation, and remodeling. Some wounds exhibit impaired healing and include delayed acute wounds and chronic wounds. Failure or disturbance in the normal stages of the healing process leads to several complications and long recovery period [2].

Some studies for assessment and diagnosis of socket healing classified the socket complications into 3 groups which included dry socket, acutely inflamed socket and acutely infected socket. Dry socket is characterized by persistent or increased postoperative pain in and around the extraction site. It is accompanied by partially or totally disintegrated blood clot or an empty socket with or without halitosis. The diagnosis is confirmed when extremely sensitive bare bone is encountered by passing a small curette into the extraction wound. Acutely inflamed socket is characterized by painful socket with exuberant inflamed tissue, but without pus or systemic fever. Acutely infected socket characterized by painful socket with suppuration, erythema, and oedema with or without systemic fever [3-5].

One study aimed to predict the healing results following tooth extraction in medically compromised patients and evaluated it by using an Adapted-University of Connecticut osteonecrosis numerical scale (A-UCONNS). The healing status of the socket was classified into 3 categories according to the duration and symptoms of the healing process. The 3 categories included normal healing, delayed healing, and MRONJ. Normal healing occurred through 10 days and showed no symptoms. Delayed healing occurred between 2 to 8 weeks and characterized by pain, bleeding, redness, and an open socket that eventually healed. MRONJ which continued for more than 8 weeks and characterized by pain, bone sequestration, and an absence of healing or epithelialization[6].

The healing of the extraction socket and the final outcome can be influenced by many factors such as: local, systemic, iatrogenic, and even environmental factors [7, 8].

Local factors have direct influence on the characteristics of the wound itself and can interrupt the socket healing, such as infection, ischemia, necrotic tissue, foreign

material, hypoxia, and bleeding. The oral cavity is a specialized environment and the healing occurs in an oral fluid containing millions of microorganisms. Systemic factors relate to the health condition of the patient which affects the ability of the body to heal such as: age, sex, diabetes mellitus, corticosteroids, thyroid disorders, blood disorders, liver diseases, renal diseases, autoimmune diseases, immunosuppressive drugs, osteoporosis, MRONJ, smoking, alcoholism, malnutrition, radiotherapy, and chemotherapy [2, 9, 10].

Hypothyroidism affects bone healing and leads to reduction in recruitment, maturation, and activity of bone cells which results in reduction of bone turnover by slowing down the process of bone resorption and formation leading to impaired bone healing [11,12]. Hypothyroidism leads to reduced angiogenesis, slow reepithelialization, and reduced expression of vascular markers such as vascular endothelial growth factor (VEGF) leading to reduction in the process of vessels branching, maturation, and stabilization. Hypothyroidism has an inhibitory effect on wound healing and angiogenesis due to decrease in metabolic activity in fibroblasts leading to high risk of infection specially with prolonged exposure of the unhealed tissue to pathogenic microorganisms [13, 14].

Diabetes Mellitus leads to impairment in the process of wound healing due to some serious complications such as hypoxia, fibroblast dysfunction, reduced host immune response, and neuropathy. Diabetes Mellitus leads to vascular problems such as poor angiogenesis and poor neovascularization, in addition to sclerosis, and obstruction of arteries and veins resulting in decreased blood flow and severe complications [2, 15].

Chemotherapy has several complications such as inhibiting cellular metabolism, cell division, fibroblast proliferation, and angiogenesis resulting in impaired wound healing process in addition to immunosuppression and decrease in the macrophages and neutrophils activity leading to easy infection [16, 17].

Radiation to the jaw bone results in development of osteoradionecrosis of the jaw (ORN). Multiple theories have been proposed to explain the mechanism of ORN. Meyer (1970) first theorized that the cause of ORN is attributed to radiation, trauma and infection, on the other hand, Marx (1983) attributed the cause of ORN to a triad of hypoxia, hypocellularity and hypovascularity [18-20], while Delanian and Lefaix (2004) proposed their fibroatrophic theory or radiation-induced fibroatrophic theory and attributed ORN to the activation and dysregulation of fibroblastic activity which leads to atrophic tissue within a previously irradiated area [21, 22].

The pathophysiology of medication-related

osteonecrosis of the jaw (MRONJ) is attributed to many factors such as impaired immune response, ineffective bone remodeling, deficient angiogenesis, prolonged wound healing, infection, and chronic inflammation [23].

Vitamin D levels have a direct relation with the healing process of hard and soft tissues. The levels of Vitamin D were classified as adequate (>30 ng/mL), inadequate (20–30 ng/mL), or deficient (<20 ng/mL). Vitamin D plays a significant role in the healing process by its effect on the immune response, inflammation process, cell proliferation and differentiation, angiogenesis and collagen synthesis [24, 25].

Oral contraceptives can lead to slower healing of oral wounds and increase oral inflammation. The estrogen in contraceptive pills leads to an increase in plasminogen activator level and in fibrinolytic activity which causes dissolution of blood clot needed for healing process. A meta-analysis (2022) reported that women that take oral contraceptives were approximately twice as likely to suffer from alveolar osteitis following a third molar extraction, compared to those not taking them [26].

Pentoxifylline was approved in 1984 by the FDA. Pentoxifylline was used to ameliorate claudication symptoms, unfortunately subsequent studies have shown that pentoxifylline and placebo have similar effects in treating claudication problems and it was not recommended for peripheral arterial diseases [27-30]. However, a network meta-analysis revealed and reported that pentoxifylline is effective and useful for symptomatic treatment of intermittent claudication [31-33]. Pentoxifylline is a vasoactive agent that leads to reducing blood viscosity, enhancing the ability of blood to flow through peripheral vessels, increasing peripheral tissue oxygenation, inhibiting fibroblast proliferation, and inhibiting collagen deposition. Multiple studies demonstrated that pentoxifylline has many properties as anti-inflammatory, anti-fibrotic, and hemorheological effect [31]. It has off-label uses for other conditions based on its anti-inflammatory and circulation-enhancing properties such as venous leg ulcers [34], neuropathic pain secondary to diabetic neuropathy [35], diabetic foot ulcers [36], and osteoradionecrosis of the mandible [21].

Pentoxifylline (PEN) was first used by Delanian and Lefaix in 2004 to treat ORN. They postulated that high dose radiotherapy leads to ORN and (RIF) "radiation-induced fibro atrophic mechanism" which results in activation and dysregulation of fibroblastic activity resulting in atrophic tissue formation within a previously irradiated area. These changes can be reversed by new combined therapy of Pentoxifylline and Tocopherol (vitamin E) to act synergistically as potent antifibrotic [20]. This theory postulates that radiation develops reactive oxygen species that subsequently result in endothelial cell injury, vascular thrombosis, and local ischemia leading to tissue loss. Pentoxifylline

improves blood flow by decreasing blood viscosity and increasing erythrocyte flexibility which facilitates their passage through microcirculation and improves tissue perfusion. Tocopherol is an antioxidant that scavenges reactive oxygen species and decrease fibroblast dysregulation [22, 37, 38]. Beneficial preventive effects of vit E have been found in some diseases such as: neurodegenerative disorders, Alzheimer's disease, atherosclerosis, and cardiovascular diseases [39].

Pentoxifylline or Vit E alone proved unable to reverse the human RIF. Their joint action might be beneficial to make them excellent antifibrotic synergistic effect [22, 40]. The combination of pentoxifylline and Tocopherol (PTX-Vit E) characterized by antioxidant pathway and synergy which help reverse ORN by decreasing the microscopic RIF associated with the progressive necrotic process and by stimulating osteoblastic healing [41].

Drug dosages were prescribed based on literature reports by different authors. Pentoxifylline dose was determined to avoid severe adverse cardiovascular effects. Tocopherol dose was designed to supply sufficient antioxidant activity. The duration depends on the case [39].

Pentoxifylline was successfully used for treatment of recurrent aphthous stomatitis as an adjunctive therapy along with the other drugs and not as the first choice. The use of Pentoxifylline can reduce the pain severity, the size and number of ulcers in the cases of recurrent aphthous stomatitis [42, 43].

Pentoxifylline was used to manage oral submucous fibrosis (OSMF). Some studies found it as an effective adjunctive therapy to improve some symptoms of OSMF such as, pain associated with the lesion, burning sensation, opening of the mouth, tongue protrusion, and difficulty in speech and swallowing [44-46]. While other studies did not recommend its use [47]. A Systematic Review and Meta-Analysis indicated that Pentoxifylline did not show a significant advantage in OSMF management when compared to other treatment modalities. However it may help reduce the burning sensation to provide some relief and improve quality of life [48].

PENTO protocol was utilized in the management of ORN. The development of PENTO therapy was dependent on the fibroatrophic theory for the pathogenesis of ORN, which was described by Delanian and Lefaix [22]. A lot of studies proposed that the prophylactic use of PENTO may improve oral mucosa healing, reduce postoperative pain and prevent ORN in irradiated head and neck cancer patients needing dental extractions [21].

PENTO protocol was used for management of MRONJ to reduce or avoid surgical intervention. It

can relieve painful symptoms, result in significant new bone formation and complete remission in some cases [49, 50]

Conclusion

Findings of the presented case and current literature suggest that PENTO protocol may be a promising treatment modality in management delayed wound healing. It is safe and cost-effective protocol. More prospective studies can be carried performed further to validate these findings.

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