

The Efficacy of Erythropoietin Mouthwash in Prevention and Treatment of Oral Mucositis in Head and Neck Cancer Patient Receiving Radiotherapy

Alaa Hosney Fahmy Hashem^{1*}, Emad Saad Mahmoud¹, Ibrahim Mahmoud Mwafey¹, Tamer Mahmoud Samy²

¹ Oral Medicine, Periodontology, Oral Diagnosis and Dental Radiology Department, Faculty of Dentistry, Assiut University, Assiut, Egypt

² South Egypt Cancer Institute, Assiut University, Assiut, Egypt

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ABSTRACT

Oral mucositis remains one of commonly clinically significant complications of chemotherapy and radiotherapy, particularly in cases with head and neck cancer. It is described by mucosal inflammation, erythema, ulceration, and severe pain, which may interfere with oral intake, nutrition, oral hygiene, and quality of life. This narrative review summarizes the potential role of erythropoietin (EPO) in the prevention and treatment of oral mucositis. EPO, traditionally recognized as the key regulator of erythropoiesis, also exhibits important non-hematopoietic effects, including anti-inflammatory, antioxidant, cytoprotective, angiogenic, and tissue-regenerative properties. Through activation of erythropoietin receptors on epithelial and endothelial cells, EPO may reduce pro-inflammatory cytokines, oxidative stress, and apoptosis while promoting epithelial regeneration and neovascularization. These mechanisms suggest that EPO may limit mucosal injury, reduce ulcer formation and pain, and accelerate healing following cancer therapy. Experimental and emerging clinical evidence indicates that EPO could represent a promising therapeutic approach for radiation- and chemotherapy-induced oral mucositis. However, concerns regarding its systemic hematopoietic effects and the limited availability of high-quality clinical evidence remain important challenges. Modified EPO formulations with reduced erythropoietic activity may provide a safer approach while preserving its tissue-protective effects.

Keywords: Erythropoietin, Mouthwash, Prevention, Treatment, Oral Mucositis, Head, Neck, Cancer, Radiotherapy

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INTRODUCTION

Mucosal inflammation frequently occurs as an immediate effect in cancer cases undergoing chemotherapy. In scenarios involving the neck and head, when the radiation zone encompasses the salivary glands and oral mucosa, radiotherapy (RT) alone or in conjunction with chemotherapy (CHT) is often the preferred treatment. Oral mucositis has been stated in cases with head and neck cancer (HNC) receiving chemotherapy (CHT) and radiotherapy (RT), influencing approximately forty percent and eighty percent of cases, respectively, regardless of CHT administration (1, 2).

Several therapy parameters have been demonstrated to influence the length and intensity of mucositis, such as the location and dosage of radiation, along with the kind and quantity of cytotoxic drugs (3, 4). Significant clinical repercussions of OM encompass discomfort, heightened susceptibility to infection, compromised nutritional absorption, and prolonged hospital stays (5). Mucosal injury is a complex process that arises from harm to epithelial cells, varying from little inflammation to severe ulceration.

The primary catalyst for mucositis appears to be the production of oxidative stress and reactive oxygen species (ROS) resulting from chemotherapy or radiation. Moreover, subsequent to the commencement of OM by ROS (6, 7).

Consequently, the application of antioxidant and anti-inflammatory substances may prove beneficial in diminishing the occurrence or intensity of this adverse effect. Numerous studies suggest that antioxidant medications offer certain advantages in the prevention of oral mucositis caused by chemotherapy and/or radiation therapy. (8, 9)

Erythropoietin (EPO), a hematopoietic agent, is predominantly synthesized in the kidneys through an oxygen-detection process and promotes red blood cell formation by activating the growth of erythroid progenitors in the bone marrow (10, 11). Recombinant human erythropoietin is utilized therapeutically for the management of anemia (12).

EPO serves as a powerful anti-inflammatory cytokine in the context of inflammatory conditions and infectious diseases, including chemical-induced tissue injury. EPO diminishes reactive oxygen species, therefore functioning as an antioxidant. (16, 17).

*Author for Correspondence: Alaa Hosney Fahmy Hashem

The objective of this review was to evaluate the efficacy of erythropoietin mouthwash in the prevention and management of oral mucositis in head and neck cancer cases undergoing radiotherapy, in comparison to a placebo-controlled trial.

Radiotherapy

Radiotherapy is a commonly employed therapeutic approach for HNC, utilized either independently or in conjunction with chemotherapy. HNC encompass tumors of the oral cavity, larynx, pharynx, paranasal sinuses, salivary glands, and nasal passages. The majority are squamous cell carcinomas originating from the epithelial lining of these areas. (18,19)

Patients receiving head and neck RT may develop acute and chronic soft-tissue changes, sensory disturbances, deterioration of dental and periodontal health, and an increased risk of osteoradionecrosis (20).

Indications

Radiation therapy constitutes a vital element of cancer management, with approximately fifty percent of all cancer patients undergoing this treatment during their illness; it accounts for forty percent of curative interventions for cancer. The primary objective of radiation therapy is to inhibit the proliferative capacity of cancer cells. (21,22).

Effects of Radiation Therapy

Radiation treatment kills tumor cells mainly by damaging their DNA. Since tumor cells usually divide more rapidly than normal cells, they are generally more sensitive to radiation. However, normal tissues are also affected, so the radiation dose and treatment area must be carefully balanced to achieve tumor control while minimizing normal tissue toxicity. This is known as the therapeutic index (23,24).

Early radiation damage mainly affects quickly dividing tissues like the skin and gastrointestinal tract. Damage to stem cells can cause loss of the protective tissue barrier, but these tissues usually recover within a few weeks through compensatory regeneration. If acute damage does not heal completely and persists, it can become a consequential late effect, especially when radiotherapy is combined with chemotherapy (25).

Late radiation complications mainly affect slowly dividing tissues like the brain, kidney, liver, intestine, fat, and muscle. These complications may include necrosis, atrophy, vascular damage, fibrosis, telangiectasia, and secondary cancers. The degree of radiation injury depends on factors like tissue sensitivity, total dose, irradiated volume, dose per fraction, acute toxicity, and combination with surgery or chemotherapy. (26).

TD 5/5 and TD 50/5 describe radiation doses associated with severe complications occurring in 5% and 50% of cases, respectively, within five years. Fraction size is considered one of the most important factors affecting late radiation toxicity (27).

Complications

Radiotherapy for HNC can cause several acute and late complications. Oral mucositis is very common and usually begins after 2–3 weeks as redness of the oral mucosa, progressing to ulceration and pseudomembrane formation with increasing radiation dose. Oropharyngeal

candidiasis is also common and may cause pain, taste changes, dysphagia, and reduced oral intake, affecting nutrition (28).

Mucosal pain and taste dysfunction can result from inflammation, ulceration, atrophy, neuropathy, and secondary infection. Taste changes occur in more than seventy-five percent of cases receiving RT and may recover within 2–6 months, although they can sometimes persist. Dental caries and periodontitis become more common mainly because of reduced saliva and changes in the oral microbiome; periodontitis may also contribute to osteoradionecrosis (29).

Xerostomia (dry mouth) is a major complication caused by damage to the salivary glands. It starts during treatment and may improve gradually over 1–2 years, depending on the radiation dose received by the glands. Late effects may include fibrosis, lymphedema, trismus, temporomandibular problems, and difficulty with tongue movement and swallowing due to fibrosis of muscles and surrounding tissues (30,31).

Oral Mucositis

Oral mucositis (OM) is a common complication of radiotherapy, chemotherapy, or both, especially in HCN and stem cell transplantation. It causes oral redness, inflammation, ulceration, and pain and can become severe enough to limit or interrupt cancer treatment. In neutropenic patients, mucositis may also increase the risk of serious infections and septicemia.

About 40% of patients receiving chemotherapy develop mucositis, usually 5–7 days after treatment begins, while the incidence rises to 90–100% when chemotherapy and radiotherapy are combined. Symptoms involve severe pain, difficulty swallowing, weight loss, taste changes, and secondary infections (32).

Mucositis can be direct or indirect. Direct mucositis occurs because oral epithelial cells have a rapid turnover of about 7–14 days, making them highly sensitive to cytotoxic treatment. Indirect mucositis results mainly from bacterial or fungal infections (33,34).

Risk Factors

Cases with HCN and those receiving high-dose chemotherapy are at high risk of oral mucositis. Risk increases with higher treatment doses and is also influenced by age, body mass, gender, genetics, and tumor location. Tumors directly exposed to radiation, such as tongue cancer, have a higher risk.

Pathogenesis

Stage 1 – Initiation: Radiation and chemotherapy cause DNA damage and ROS production, leading to epithelial cell death.

Stage 2 – Primary Damage Response: Activation of pathways such as NF- κ B, p53, Wnt, and MAPK causes inflammation and further cell damage.

Stage 3 – Signal Amplification: Inflammatory mediators such as TNF amplify tissue inflammation and injury.

Stage 4 – Ulceration: Damage to the epithelium produces painful ulcers, which may be colonized by bacteria and worsen inflammation.

Stage 5 – Healing: Epithelial cells migrate, proliferate, and differentiate, allowing the mucosa to repair and heal (35).

Grading and Scoring Scales

Several scales are used to assess oral mucositis severity. The WHO scale evaluates symptoms, mucosal changes, and ability to eat, while RTOG assesses acute radiation damage and NCI-CTCAE focuses on symptoms and functional impairment. In the WHO scale, Grade 1 includes soreness and erythema without ulcers with normal diet; Grade 2 includes erythema and ulcers but solid food is tolerated; Grade 3 involves extensive ulcers with inability to swallow food; and Grade 4 is severe mucositis with inability to eat orally(36).

According to the NCI-CTCAE/CTCAE v5.0, Grade 1 is asymptomatic or mild mucositis requiring no intervention. Grade 2 causes moderate pain or ulcers but does not interfere significantly with oral intake & may require a modified diet. Grade 3 causes severe pain & interferes with oral intake, often requiring supportive treatment. Grade 4 is life-threatening & requires urgent intervention or nutritional support, while Grade 5 indicates death related to toxicity (37).

Treatment

Pain Control: Pain from oral mucositis can reduce food intake, oral hygiene, and quality of life. Short-term relief may be provided by anesthetic mouth rinses such as 2% viscous lidocaine. 0.2% morphine and 0.5% doxepin mouth rinses may also be efficient. Although sucralfate forms a protective coating over the mucosa, MASCC/ISOO does not suggest it because of insufficient efficacy.

Photobiomodulation (PBM): Also known as low-level laser treatment, PBM utilizes low-energy red or near-infrared light to diminish inflammation and tissue damage. It has been shown to decrease the degree of oral mucositis and is suggested by MASCC for prevention of mucositis in patients receiving radiotherapy or chemoradiotherapy. Other drugs such as celecoxib, misoprostol, and rebamipide have shown some benefit, but stronger evidence is still needed (38).

Oral Hygiene and Antimicrobials

Maintaining good oral hygiene and educating patients about proper mouth care can reduce the degree of oral mucositis. During the ulcerative stage, bacterial and fungal overgrowth can worsen inflammation and may lead to bacteremia or sepsis in severe cases. Antiseptic mouth rinses are therefore commonly included in oral care programs. Chlorhexidine has been widely studied, but clinical trials have not shown clear benefit in preventing chemotherapy- or radiation-induced mucositis (39).

Growth Factors

Growth factors such as GM-CSF and G-CSF have been studied for preventing oral mucositis. They increase neutrophil activity, which may stimulate endothelial cells and keratinocytes and help protect the oral mucosa from damage caused by radiotherapy and chemotherapy (40).

Cryotherapy

Oral cryotherapy involves cooling the mouth during chemotherapy. It causes vasoconstriction, reducing blood flow and the amount of chemotherapy reaching the oral tissues, thereby potentially reducing mucosal toxicity. Evidence is mainly available for chemotherapy-induced mucositis, with some conflicting results (41).

Laser Therapy

Low-level laser therapy (LLLT) is a non-invasive treatment with anti-inflammatory, analgesic, and wound-healing effects. It promotes cell proliferation and migration and has shown consistent benefits in preventing mucositis caused by chemotherapy, radiotherapy, and chemoradiotherapy (42).

Erythropoietin (EPO)

Erythropoietin (EPO) is mainly produced by the kidneys, with smaller amounts produced by the liver and brain. Besides its role in stimulating red blood cell production, EPO has important tissue-protective and regenerative effects. In oral tissues, it may promote healing, stimulate stem cells, improve blood supply, and reduce inflammation after tissue injury (43).

In addition, EPO has potential applications in wound healing and tissue regeneration. It has been investigated in dental procedures like tooth extraction and implant placement, where it may promote healing of soft tissue and bone, particularly when normal bone healing is impaired (44).

Composition and Effects of Erythropoietin

Physical Structure: Erythropoietin is a glycoprotein made of 165 amino acids with a compact structure containing four α -helices. It is relatively stable and can retain its biological activity under high temperatures and a wide range of pH conditions.

Chemical Structure: EPO contains four glycosylation sites, including three N-linked sites that contribute significantly to its molecular mass. Its protein structure is mainly α -helical, with about 50% α -helix content and no significant β -sheet structure.

Anti-inflammatory Effects: EPO reduces inflammation by inhibiting NF- κ B and decreasing pro-inflammatory cytokines like IL-1 β , TNF- α , IL-12, IL-6, and IL-23. It also diminishes the production of ROS, giving it antioxidant and protective effects.

Healing Effects: EPO promotes tissue healing through anti-inflammatory, anti-apoptotic, cytoprotective, and pro-angiogenic effects. Since EPO receptors are present on basal cells of the oral mucosa, EPO may enhance healing of oral lesions by reducing inflammation, stimulating stem cells, improving blood supply, and promoting tissue regeneration. Therefore, it has potential as a treatment for oral ulcers and mucosal injuries (45).

Uses

EPO and erythropoiesis-stimulating agents (ESAs) are mainly utilized to treat anemia associated with chronic kidney disease and chemotherapy, helping to reduce the need for blood transfusions. They may also be used in selected cases of anemia related to cancer, chronic disease, AIDS treatment, and around surgery(46).

Dental Uses of Erythropoietin (EPO)

EPO has potential dental uses in wound healing and bone regeneration, helping repair oral mucosal injuries and improving healing after tooth extraction, periodontal surgery, and implant placement through tissue regeneration and angiogenesis. It may also support bone healing in periodontitis and dental implantology by improving blood supply and oxygen delivery.(47).

EPO may help treat oral mucositis through its anti-inflammatory, cytoprotective, and healing influences. It reduces inflammatory cytokines like IL-1 β , TNF- α , and IL-6 and protects mucosal cells from apoptosis through the JAK2/STAT5 pathway. It also promotes angiogenesis and epithelial cell regeneration, helping reduce ulceration and accelerate healing. However, further studies are required to confirm its clinical safety and effectiveness.(48).

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