Review

Topical Oxygen Therapy: A novel Strategy for Oral Healthcare

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Abstract: Worldwide, oral lesions and cancers are still being significant public health conditions. Thus, an introduction of new oral healthcare protocols is becoming essential. Oral diseases are related to many causative factors, manly dental plaque/biofilm due to poor hygiene. New anti-biofilm therapies are needed to develop. The strategies of anti-biofilm therapies should help to control biofilm formation and microbial attachment to dental surfaces. The present review aimed to provide a comprehensive over-view on evidence related to the potential utility of topical oxygen therapy (BlueM formula) as novel oral care therapies in clinical practice.

Keywords: oral care; oxygen therapy; oral biofilm; dental caries; periodontitis; peri-implantitis

1. Introduction

The general health of population is significantly impacted by the status of oral health [1]. Therefore, people should adhere to daily oral hygiene as well as sufficient professional oral-care in order to comfortably eat, talk, and retain self-esteem [2]. The World Health Organization (WHO) has reported in 2020 that oral lesions and diseases still being significant public health conditions, worldwide [3]. There is >3.5 billion patients suffering from oral diseases [3]. Dental caries is affecting >2.3 billion patients over their life. Periodontal disease is the major cause of teeth loss. It is estimated to affect 20-50% of global population [3]. Unfortunately, dental caries and periodontal diseases are still noncommunicable conditions, with significant health, social, and economic impacts. In addition, oral cancers are serious health problem worldwide, with nearly 200,000 deaths each year [3]. In recent years, peri-implantitis also becomes the most common oral disease that causing dental implants failures [4].

In most countries, oral healthcare systems are depending on dentist-centered model with high technology [3,5]. These systems do not sufficiently encourage prevention of oral diseases. In addition to prevention, early treatment of oral diseases is still not attainable for millions of patients [3,6]. Thus, the introduction of preventive tools as well as promoting oral care in public are essential for healthy lifestyles among children and adults.

Oral lesions are related to many causative factors, mainly poor hygiene [7,8]. However, dental plaque/biofilm is the main etiological factor [9]. Understanding the etiological factors for oral diseases, provides the basis for integrated strategies for prevention and control.

2. Oral health and biofilm

Oral cavity contains approximately 700 species of microorganisms (i.e., bacteria, fungi, viruses and protozoa) [10,11]. In fact, microbiome is important for maintaining the healthy system in oral

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cavity as well as gut. However, pathogenic biofilms can result from microorganisms adhering to each other and to dental surface [11].

The development of a biofilm occurs in several stages [12,13]. First, free-swimming bacteria (planktonic) form a reversible attachment to an oral surface (teeth and gums). Mainly, Streptococcus, Veillonella, Actinomyces, and Neisseria are the most common primary colonizers on dental surfaces [13]. The protein in the saliva initially binds various dental surfaces, which are then recognized by the primary colonizers that will attach to these surfaces starting synergetic relationship with more bacteria attachments that allow for the biofilm formation [13]. Then, the bacteria develop an initial layer, firmly attached, of biofilm matrix. At this point, bacteria start consuming polysaccharides (sugars from the food we eat) and form a multi-layer microcolony [13]. The microcolony builds up ver-tically as the microbes consume more polysaccharides, and more planktonic bacteria join the colony [13]. Specifically, Corynebacterium spp anchor to the primary colonizers, and then extend outward to provide a 3D structure of biofilm. Then, the oxidative species, such as Haemophilus, Aggregatibacter, and Neisseriaceae occupy the oxygen-rich periphery [13]. Most importantly, the metabolic activities of these species at the periphery creates an anoxic environment at the biofilm center, which allows more pathogenic bacteria, such as Capnocytophaga, Leptotrichia, and Fusobacterium to grow in the middle of biofilm structure [13]. Eventually, mature biofilm is formed and maintained by multiple path-ogenic bacteria.

In anoxic periodontal pocket, the Gram-negative bacteria (e.g., *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*) can grow fast and dominating the subginigval biofilm [13,14]. These bacteria are helping each other by protein-protein interactions and lectin-carbohydrate interactions allowing for the attachment of more bacteria to dental surfaces [14]. Additionally, the bacterial cells signaling and communication are very important in biofilm formation [15].

In fact, some recent studies found that oxygen therapy can inhibit the formation biofilms [16,17]. For instance, Ahn and Burne [16] found that the oxygen molecule impairs dental biofilms by *S. mutans*. Therefore, oxygen can reduce biofilm infection due to anaerobic shift metabolism are hallmarks of [18].

In 2017, a worldwide periodontal workshop successfully addressed unresolved issues related to the types of periodontal diseases, progression, and pathogenesis [19,20]. Over the last 100 years, the understanding of periodontal pathogenesis and associated etiological factors has been went through several stages and concepts as in Figure 1.

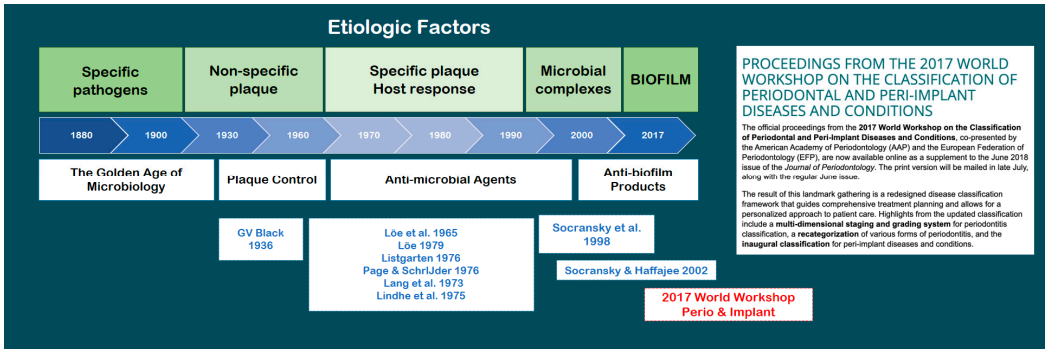

Figure 1. History of >100 years to understand the 'etiologic factors' of periodontal diseases.

Eventually, it becomes evident that the supra- and subgingival biofilm associated with gingivitis and periodontitis starts from a collection of commensal organisms that coexist in relative harmony. Then, a shift in the microbial composition within biofilm (dysbiosis) might occur and result in the overgrowth of more virulent bacteria [20]. This leads to exacerbate periodontal inflammation, infection, and tissue destruction. Therefore, the composition of oral biofilm needs to be always maintained and redirected toward a symbiotic state, which is compatible with gingival/periodontal health.

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Thus, it is still demanding to develop new therapies to control biofilm formation in oral cavity [21,22]. Besides, studies are ongoing to evaluate the potential utility of active oxygen to disrupt bacterial biofilms.

3. Conventional strategies for oral care

Over the past decades, various chemical agents have been used to manage dental biofilms [23]. Usually, these conventional antiseptic agents contain different active ingredients that recommended for specific clinical indications. In fact, 90% of the commonly used antiseptic products contain harsh antibacterial chemicals as chlorhexidine, cetylpyridinium chloride, alcohol, essential oils, iodine, peroxide, etc. [23,24]. For example, chlorhexidine (CHX) is generally the most popular antiseptic used for oral care [25]. However, it has a number of negative effects (Table 1), which have already been disclosed in many literatures [26,27].

Table 1. different levels of CXH side effects and clinical limitations.

Side effects of CHX	Ref.
Staining of teeth and calculus formation	[26,27]
Change in taste	[27]
Large molecule, difficult to penetrate deeply into biofilm	[28,29]
Cytotoxic on fibroblasts, osteoblasts, and lymphocytes	[30,31]
Allergic reactions and irritation of oral tissues	[32,33]
Shift in healthy oral microbiome, decrease in saliva and plasma nitrite, increase blood pressure	[34]
Alters surface topography of dental implants	[35]

Similar to antibiotics, these compounds have a broad range of effects and do not specifically target a pathogenic biofilm, which could lead to an increase of resistant bacteria and reduce the therapeutic effectiveness of conventional antiseptics [28]. In addition, a protective matrix of extracellular polymeric materials surrounds the harmful germs (e.g., exopolysaccharides). This matrix promotes bacterial tolerance while decreasing agent access [29]. Therefore, for an anti-biofilm therapy to be effective, both the biofilm matrix and the specific microbial cells inside it need to be targeted. As in Figure 2, CHX ($C_{22}H_{30}Cl_2N_{10}2C_6H12O_7$) is a cationic large molecule with mass of 898 Da [30].

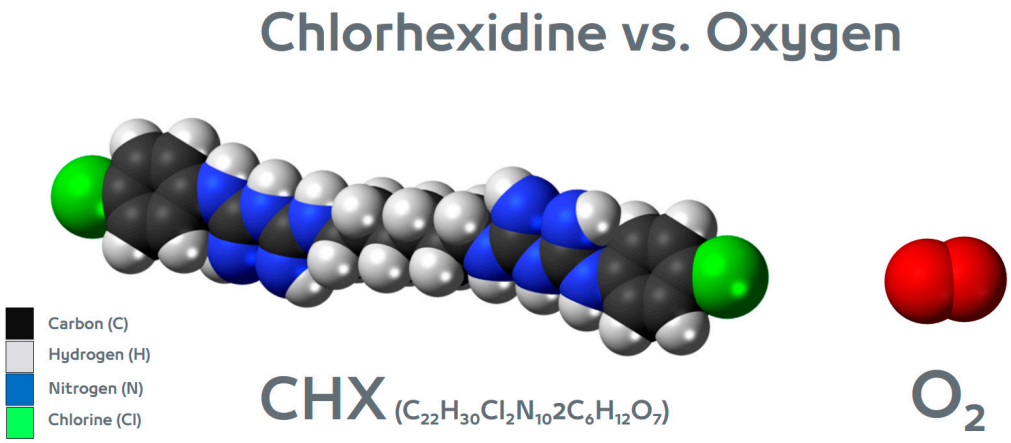

Figure 2. A diagram of large CHX molecule structure compare to small oxygen (O2) molecule.

Chlorhexidine agent can attach to the negative-charged bacteria cell surface and causing cell damage. Therefore, it is likely that CHX molecules cannot penetrate biofilms and have very little effect on the pathogenic microorganisms inside oral biofilms [29]. There is little data on the efficacy of intra-wound irrigation with conventional antiseptics. Based on some available data, CHX can

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negatively affect fibroblasts, osteoblasts, and lymphocytes, which could slow the wound healing process [31]. Moreover, few clinical reports documented tissues allergy in relation to chlorhexidine [32,33]. Bescós et al. [34] observed a negative effect of using CHX mouthwashes for long period on the level of patients' blood pressure. Finally, Krishnamoorthy et al. [35] concluded a possible negative effect of using CHX irrigation in treating peri-implantitis. CHX can alter the surface topography of dental implants, which might influence a potential of re-osseointegration.

Recently, novel therapeutic strategies have been proposed to combat dental biofilms [36]. One is the inhibition of bacterial adhesion to dental as well as implant surfaces. In fact, the primary colonizer bacteria generate physically an interface that allow the adhesion of more microbes to dental surfaces and then form biofilms [37]. By affecting the sequence of bacteria (primary colonizer) cells-adhesion, this will lead to differences in the overall biofilm development [37,38]. Second, extensive efforts have been made to develop agents with control-releasing anti-biofilm property to exert their antimicrobial activity over time in situ to prevent biofilm formation [39].

3. Topical oxygen therapy: in situ releasing of active oxygen

The use of oxygen therapy is common in medicine for almost 100 years [40,41]. It been available as treatment for hypoxemia, since discovered by Joseph Priestley in 1774 [41]. Generally, oxygen therapy can be systemic (hyperbaric) or topical. There is evidence that supplementary of systemic oxygen improves healing of wounds in different parts of the body wounds [42]. It can exert an anti-infective effect, reduce inflammation, and stimulate angiogenesis [42].

The use of oxygen as applied topically over injured tissue is not extensively discovered and remains controversial [43,44]. Indeed, it can be hypothesized that an application of topical oxygen might quickly reverse tissue hypoxia in situ [44,45]. Also, it can kill anaerobic bacteria and enhances immune cells function to address all other pathogens [45]. The increase of local oxygen level in wounded tissues can promote better healing [45].

Recently, a new topical oxygenating formula (blue®m) has been developed by Dr. Peter Blijdorp and his research group [46–48]. Clinically, blue®m formula is applied orally to prevent the growth of biofilms causing oral infections [48–50].

Chemically, as in Figure 3, blue®m formula contains manly sodium peroxoborate, glycerol, and cellulose [51]. In aqueous solution, blue®m formula produces low concentration of hydrogen peroxide, which has well-known antiseptic effect [51].

The technology by blue®m is based on controlled release of topical oxygen. In addition, the release of low concentration hydrogen peroxide has a bactericidal action [52]. Another important component of the blue®m formula is Lactoferrin which has the potential promote of bone cells [53].

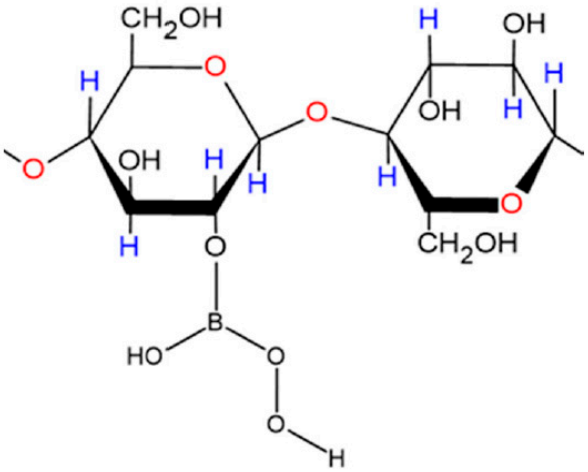

Figure 3. Hydro-carbon-oxo-borate complex in blue®m formula. Courtesy reference [51].

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As noted above, the chemistry of blue®m formula is stable and share common ingredients with the available commercially products. Interestingly, blue®m formula can slowly release active oxygen, without generating hydroxyl radicals. The release of oxygen from blue®m products is favoring the 5 pillars of oxygen therapy, as following: 1) increases cellular metabolism, 2) increases collagen synthesis, 3) facilitates the release of growth factors, 4) stimulates angiogenesis, and 5) has bactericidal action [54].

4. Clinical applications of blue®m oxygen therapy and initial protocols

For dental application, Dr. Peter Blijdorp was the first to suggest TOOTh directive (Topical Oral Oxygen Therapy) protocol for oral healthcare, as in Figure 4.

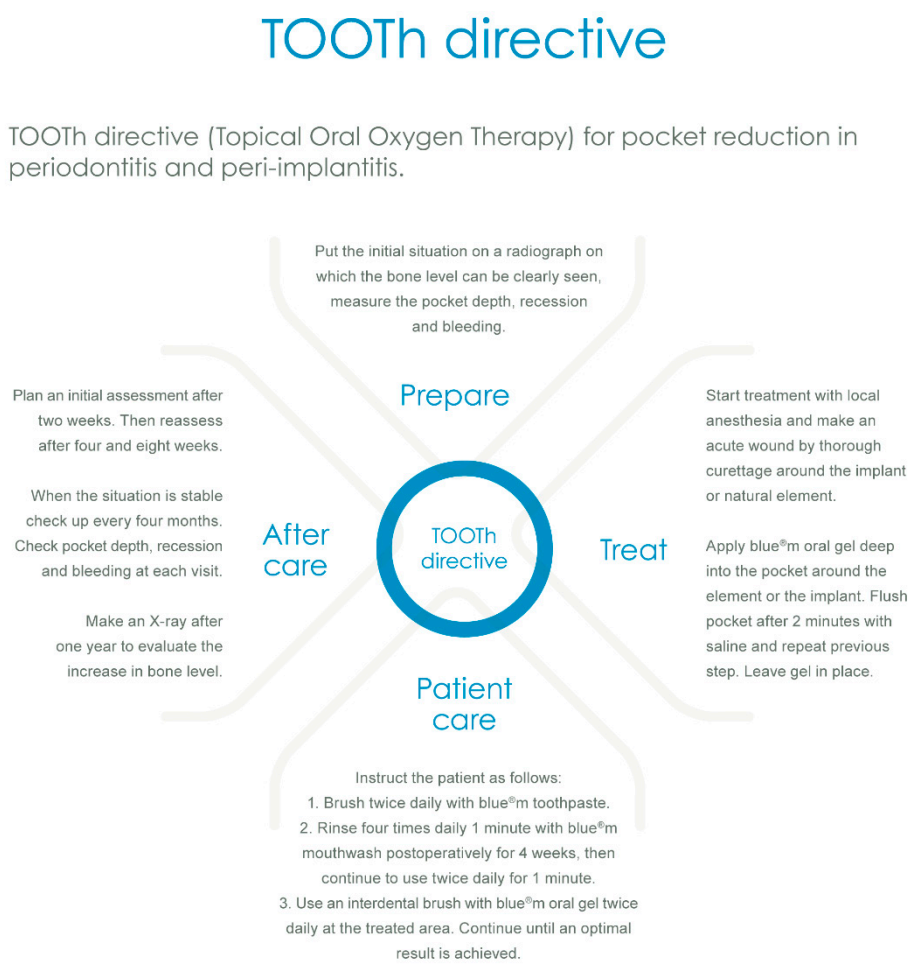

Figure 4. A scheme of TOOTh directive (Topical Oral Oxygen Therapy) for oral healthcare.

Such clinical protocol aims to offer a significant strategy to control biofilms associated oral infections. Secondly, the release of oxygen in situ should assist the healing of oral tissues and wound oxygenation [55].

4.1. Control of dental caries

Tooth decay is commonly caused by the action of *S. mutans* on dental surfaces. Therefore, new substances are continually developed and studied in order to control *S. mutans* biofilm causing tooth decay. For instance, Ntrouka et al. [56] confirmed that oxygenating agent was significantly effective in controlling S. mutans biofilms. Currently, Santos et al. [57] evaluated the antimicrobial capacity of blue®m formula against S. mutans and its virulence factors, e.g., gbpA gene expression. The study

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findings supported the preventive potential of BlueM oxygen agent on the control of oral biofilm related dental caries.

Besides, chlorhexidine is sometimes used by dentists to disinfect dental cavities before placing the restorative material. However, its negative impact on the adhesion of dental restoration is still unclear. Also, CHX showed to cause gingival margin gaps of Class-V giomer restorations [58]. Other disinfectants such as the oxygen-containing agents may be promising alternatives, but need further studies to prove their clinical viability as cavity disinfectants.

4.2. Gingival and periodontal healthcare

The healthy condition of periodontal tissues can be influenced by changes in biofilm homeostasis (Figure 5).

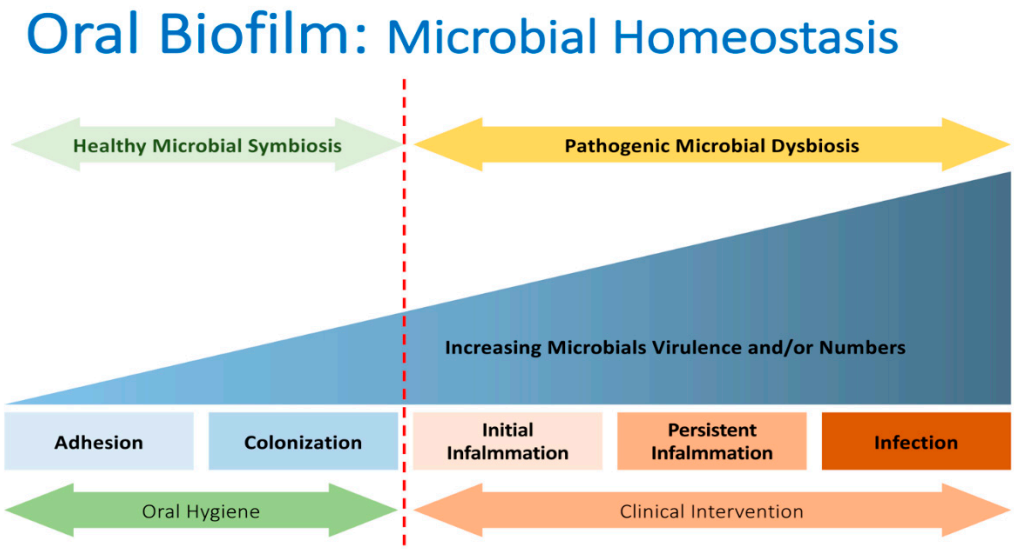

Figure 5. An illustration of microbial homeostasis in oral biofilm (Symbiosis vs Dysbiosis).

In fact, the inflammation in gingiva 'Gingivitis', and then tissue destruction 'Periodontitis', is related to changes in microbial homeostasis (i.e., dysbiotic). Therefore, it has been suggested that an oxygen therapy by blue®m can be helpful to restore and maintain healthy homeostasis of oral microorganisms. For example, the results by Mostajo et al. [59,60] expressed a significant shift in microbial composition toward a homeostasis state of biofilm after applying oxygen therapy.

Deliberador et al. [48] showed a strong effect of blue®m oxygen therapy on *P. gingivalis*. Also, Niveda and Kaarthikeyan [61] performed a clinical trial on patients suffering from moderate to severe chronic periodontitis. Their treatment protocols involved blue®m oxygen therapy. There was a significant reduction in probing pocket depth from baseline to 6-weeks. Indeed, this confirmed the clinical advantage of blue®m oxygen therapy on periodontitis [62]. In another clinical study, Cunha et al. [63] demonstrated a remarkable effect of blue®m oxygen therapy on gingival inflammation.

Clinically, we presented a number of case scenarios using blue®m oxygen therapy, as following:

4.2.1. Clinical scenario

In Figures 6 and 7, a clinical case was carried out and conducted by Dr. Marcelo Imano (Curitiba/PR, Brazil). A 36-year-old female was diagnosed with generalized aggressive periodontitis. For treatment protocol, non-surgical periodontal therapy in addition to blue®m oxygen therapy were performed. The gel was applied 4 times on consecutive days, the first application being followed by scaling and root planing. Clinical follow-up was performed at 15, 30, and 60 days and 5 years. At a recall of 5 years (Figure 8), the patient is currently under control and undergoing supportive periodontal treatment every 4 months.

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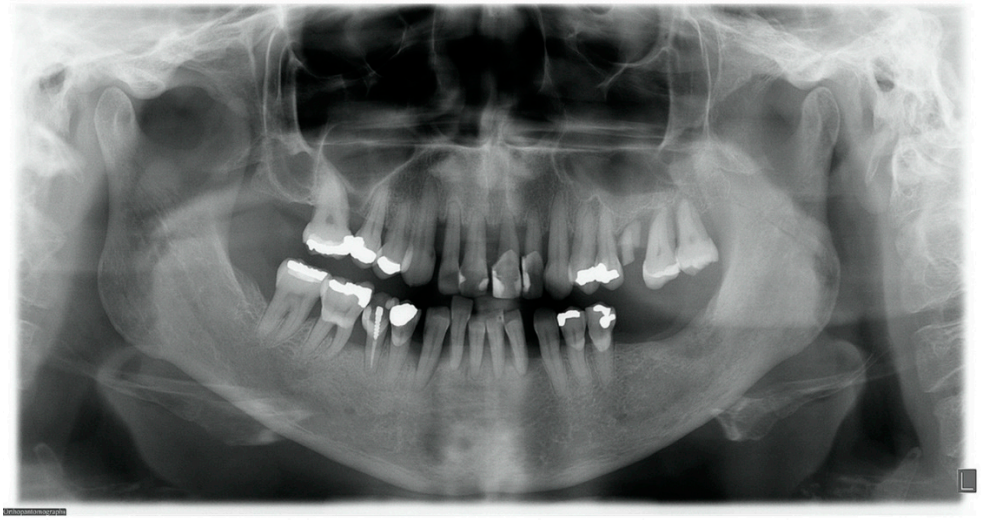
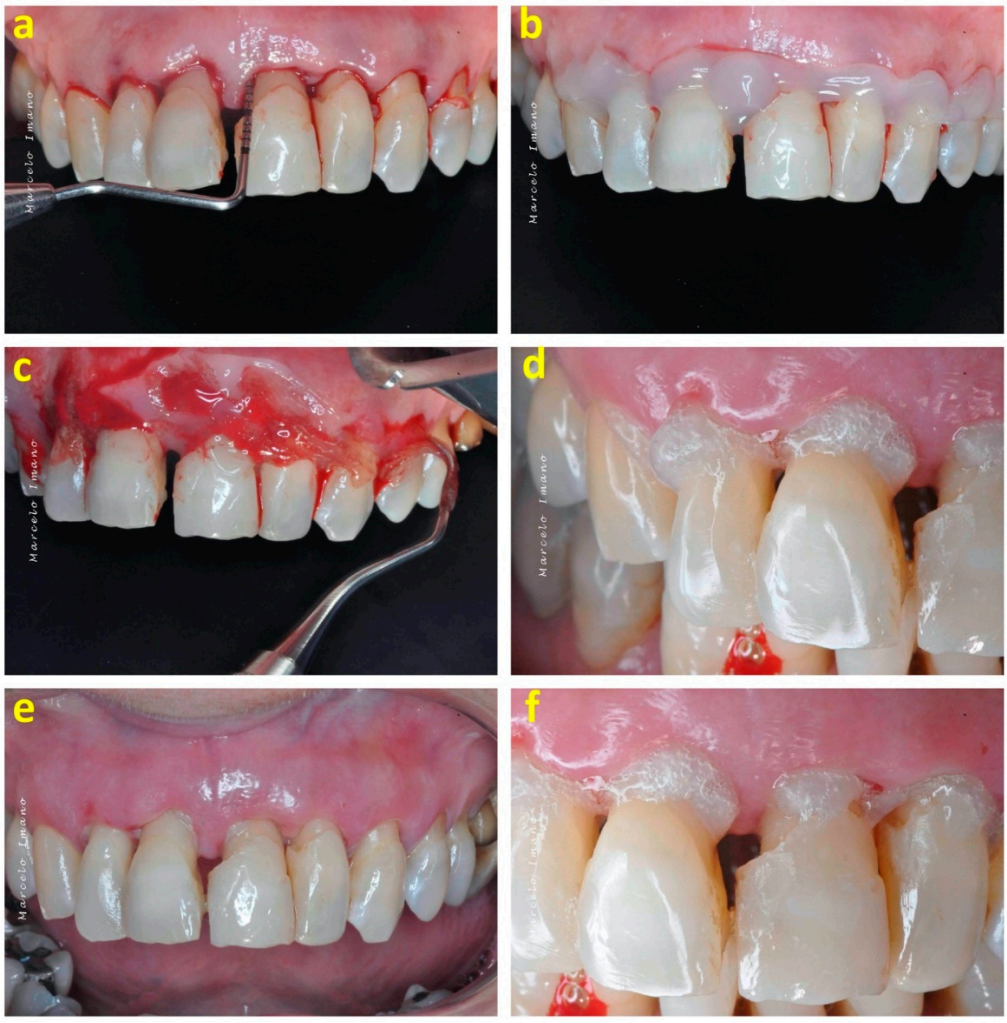


Figure 6. Initial panoramic X-ray, bone loss is observed and the teeth 26, 27 and 28 were indicated for extraction.



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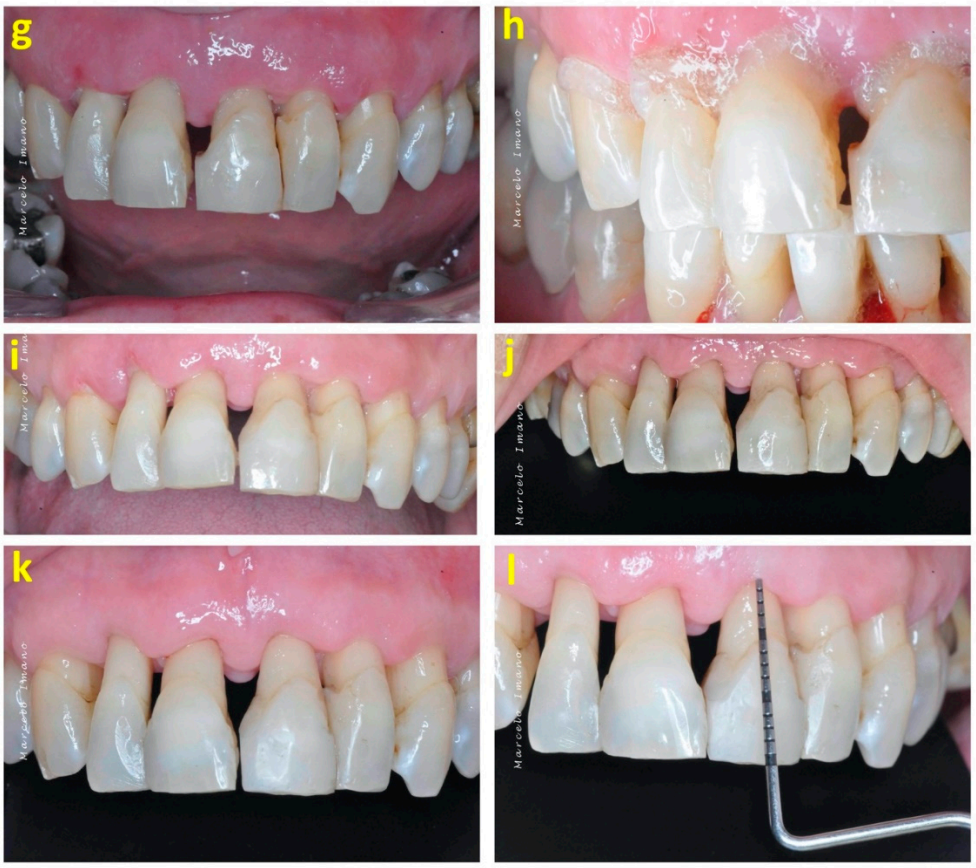

Figure 7. In these clinical images: (a) initial clinical examination showed bleeding on probing, probing depth (>5 mm), and clinical attachment loss (>40%). Diagnosis: generalized aggressive periodontitis. (b) supra and subgingival scaling and root planing, then application of blue®m oral gel. It was introduced inside the periodontal pockets and around the teeth. The gel was kept in place. (c) few seconds after applying the gel. (d) it is possible to observe the bubbles that show the release of oxygen topically. (e) one-day post-therapy using blue®m gel. (f) second application of blue®m oral gel. (g) two-days post-therapy using blue®m oral gel. (h) third application of blue®m oral gel. (i) three-days post-therapy using blue®m oral gel. (j) follow-up after 15-days. (k) follow-up after 30-days. (l) follow-up after 60-days. Status of periodontal tissues showed healthy, with no bleeding on probing, reduced probing depths (1 to 4 mm) and excellent plaque control.

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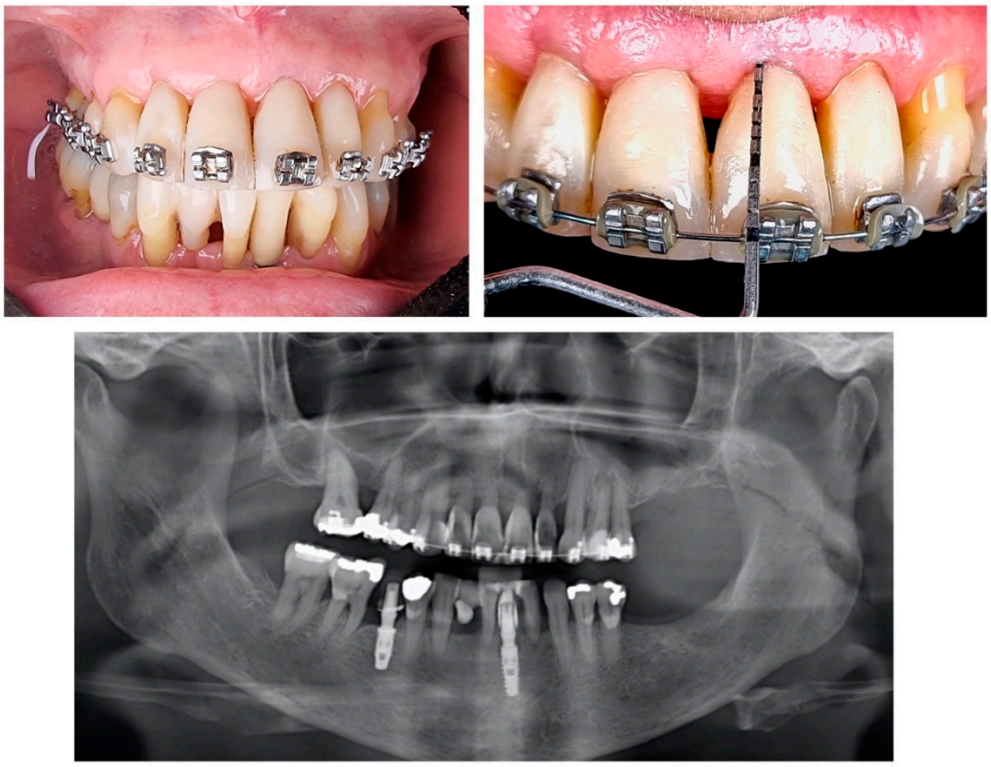

Figure 8. Clinical and Panoramic X-ray of 5-years recall. Patient underwent orthodontic treatment and lower rehabilitation with two implants. Periodontal tissues were healthy, with no bleeding on probing, reduced probing depths and excellent plaque control.

4.3. Dental implants: health and diseases

In healthy status, a peri-implant mucosa is healed around the implant abutment. While, bone tissue is maintaining a direct contact to the implant surface (called osseointegration). Similar to periodontal tissues, inflammation can affect the tissues surrounding dental implants (peri-implantitis), which may cause implant failure.

A microbiology study by Pérez-Chaparro et al. [64] showed similar pathogens (*P. gingivalis, T. denticola* and *T. forsythi*) are related to the etiology of periodontitis and peri-implantitis.

When applying blue®m oxygen therapy on a subgingival biofilm (contain periodontal pathogens), the results showed an excellent selective effect compared to chlorhexidine [50]. Also, the periodontal bacteria had a significant loss of their ability of biofilm formation. Thus, more studies are needed to assess the clinical advantages of blue®m oxygen therapy with dental implants.

4.3.1. Clinical scenario

Figure 9 is presented by Dr. Alex Oliveira de Moura from (Fortaleza/CE, Brazil) uder supervision of Professor Tatiana Deliberador (Curitiba/PR, Brazil). Peri-implant mucosa got diseased due to poor oral hygiene and caring of lower prosthesis supported by dental implants. The prosthetic denture was removed and instructed patient to apply blue®m oral gel 3 times a day during the 7 days. Finally, healthy condition of peri-implant tissue was retrieved and maintained.

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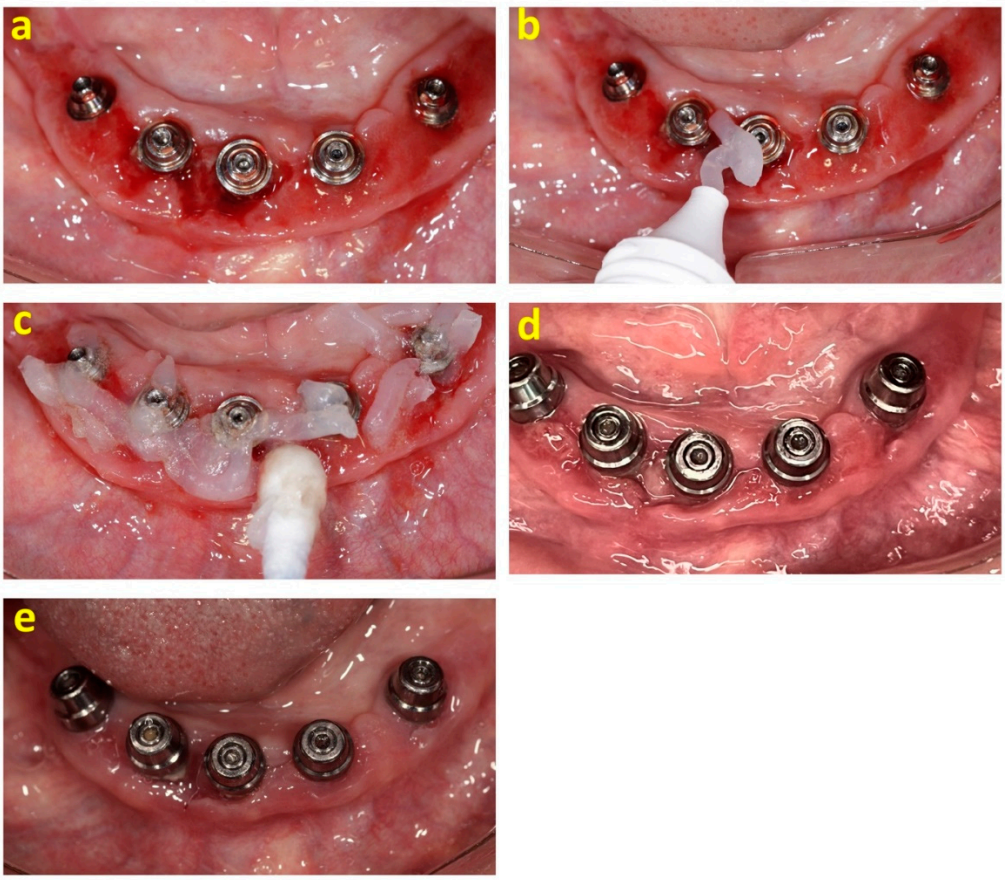

Figure 9. In these clinical images: (a) clinical appearance of peri-implant tissue after removal of prosthesis. Gingival inflammation and bleeding on probing were detected. The probing depth was between 2 to 4 mm. Diagnosis of peri-implant mucositis. (b&c) application of oxygen blue®m gel. The gel was gently spread throughout the inflamed region. Observe the oxygen bubbles being released. (d) follow-up after 48 hours. (e) follow-up after 7 days. Healthy appearance of the peri-implant tissues.

4.3.2. Clinical scenario

Another clinical implant case (Figure 10) by Dr. Minas Leventis (University of Athens, Greece). An application of blue®m oxygen therapy was used for healing abutment and sutures materials. Three weeks after uncovering, the soft tissues showed excellent healing and matured around the healing abutment. Then, the implant was successfully restored with a screw-retained crown.

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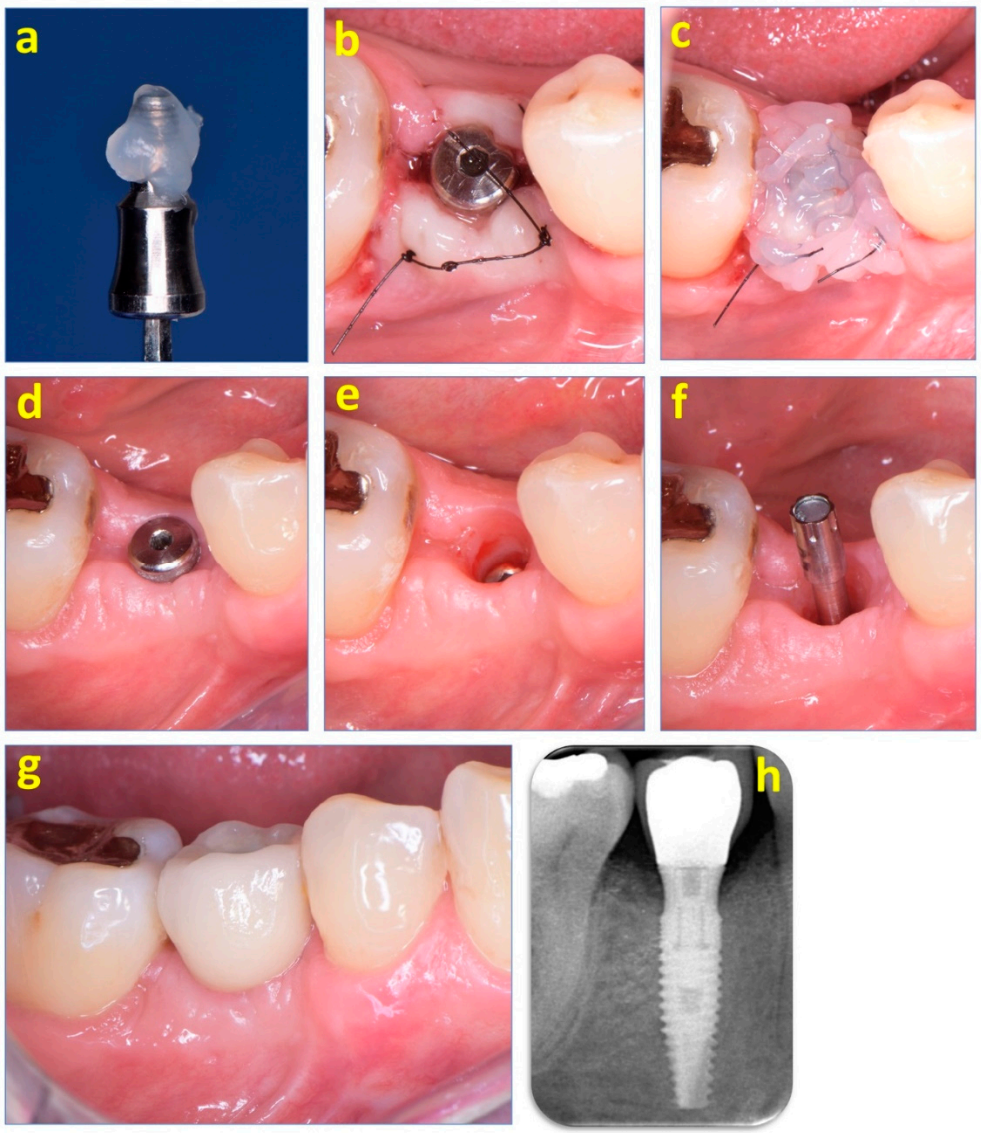

Figure 10. In these clinical images: (a) using blue®m oxygen therapy for healing abetment. (b&c) blue®m oxygen gel was also performed on top of sutures. (d&e) 3-weeks later, the soft tissues showed excellent healing around healing abutment. (f) Penguin ISQ measurement revealed high secondary stability of the implant (ISQ = 75). Then, implant was successfully restored with a screw-retained crown. (g&h) after 6 months, clinical evaluation revealed a pleasant esthetic outcome.

4.4. Management of oral lesions

The common oral lesions include traumatic lesions, aphthous ulcers, lichen planus, angular cheilitis, herpes infection, mucocele, and xerostomia [65,66]. A definitive diagnosis is necessary to manage oral lesions, correctly. Treatment is usually palliative and supportive. Relief of pain, inflammation, and ulceration are the main goals of therapy [66]. Medications can include topical corticosteroids, analgesics, and antimicrobials (e.g., topical oxygen therapy). For instance, a significant improvement in Lichen planus lesions after applying topical corticosteroids and blue®m oxygen therapy was published [67].

Mattei et al. [47,49] used blue®m oxygen therapy to reduce postoperative pain, successfully. In addition, blue®m oxygen therapy favors the healing of large cystic lesions in mandible [68].

4.5. Care of oral wounds

In fact, the oxygen level in wounded tissues plays an important role in healing. Oxygen is vital for angiogenesis and cellular functions. Therefore, the application of blue®m oxygen therapy is

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showing many clinical advantages on oral wound healing [55]. Also, it can favor tissue oxygenation as well as regeneration [55]. Moreover, blue®m oxygen therapy is a promising to control clinical complications and pain after oral surgeries [69].

Additionally, it's interesting to note that the slow release of oxygen by blue®m can aid the deep cleaning and decontamination of deep soft and bone tissues. Also, by increasing the oxygen levels in injured bone tissue or following tooth extraction, the slow oxygen release concept can hasten wound healing. However, it is required to illustrate the potential advantages of topical oxygen therapy in more clinical investigations.

4.5.1. Clinical scenario

Figure 11 is a case of flap dehiscence after implant placements and guided bone regeneration (GBR) by Dr. Minas Leventis (University of Athens, Greece). Topical application of blue®m oxygen therapy was performed on top of the surgical wound and sutures materials. After two weeks, sutures were removed. The soft tissues showed dehiscence in some areas and no complete closure of the wound. The surgical site was treated with blue®m oxygen gel in order to improve healing of wound dehiscence. One week later, an excellent secondary intention healing allowed the body to cover the area with newly-formed soft tissues. Three months post-op, uncovering process for implants was performed. The healing was uneventful and the area is covered by thick keratinized soft tissues. The architecture of the ridge is preserved.

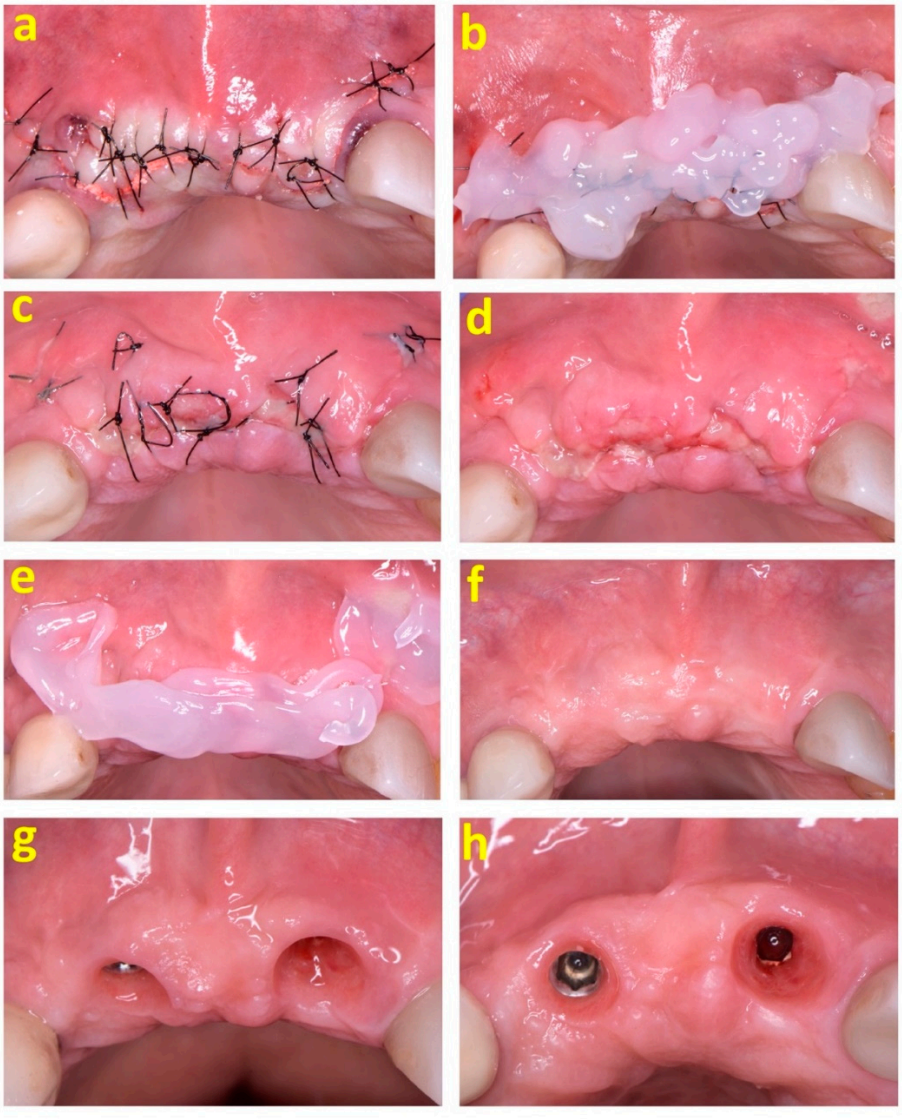

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Figure 11. In these clinical images: (a) flap closed and sutured after implant placements and guided bone regeneration (GBR). (b) topical application of blue®m oxygen therapy was performed on top of the surgical wound and sutures materials. (c&d) after two weeks, sutures were removed. The soft tissues showed dehiscence (no complete closure of the wound). (e) the surgical site was treated with blue®m oxygen gel in order to treat wound dehiscence. (f) one week later, an excellent secondary intention healing allowed the body to cover the area with newly-formed soft tissues. (g) three months post-op, uncovering process for implants was performed. (h) the healing was uneventful and the area is covered by thick keratinized soft tissues. The architecture of the ridge is preserved.

4.5.2. Clinical scenario

In this case (Figure 12), Dr. Minas Leventis (University of Athens, Greece) was conducted an access flap for surgical endodontics. A flap-design was semilunar to avoid gingival recession. Then, cystic lesion was removed. The root apex was cleaned and treated with MTA. The surgical area was refreshed with blue®m oxygen therapy for 5 minutes. Then, the site was filled with a synthetic bone material. The flap was closed and sutured. Topical blue®m oxygen gel was applied on top of the wound. Patient was instructed to continue using topical blue®m gel twice/day for one week until the sutures were removed. The blue®m oxygen therapy was continued for couples of weeks to support tissue healing. After 7 months post-op, soft tissue showed optimal healing without unpleasant scar appearance. The follow-up 4-years, clinical results observed stable status of soft tissues.

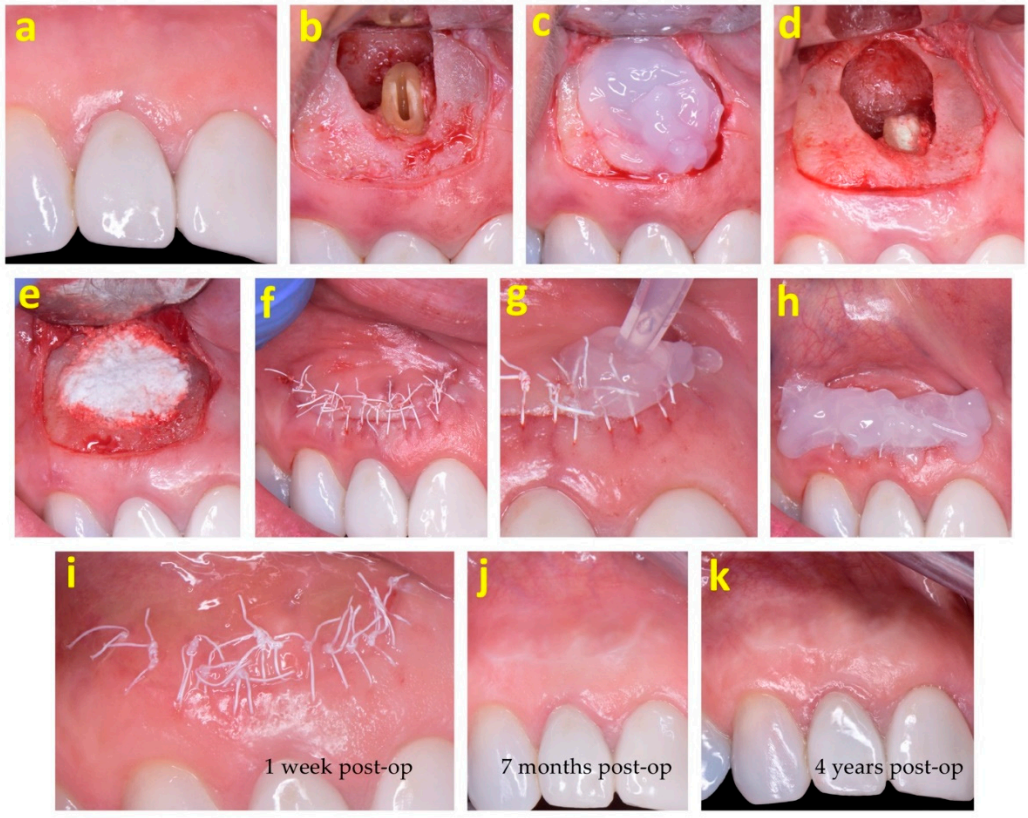

Figure 12. In these clinical images: (a) tooth #12 indicated for surgical endodontics. (b) a semilunar flap was performed to remove cystic lesion. The root apex was cleaned and treated with MTA. (c) surgical area was refreshed with blue®m oxygen gel. (d&e) the site was filled with bone materials. (f) flap was closed and sutured. (g&h) blue®m oxygen therapy was used post-op. (i) after one-week, sutures removed, and patient continued using blue®m oxygen gel at home. (j) soft tissue healing showed excellent healing without unpleasant scar appearance, after 7-months post-op. (k) follow-up 4-years, clinical results observed stable status of soft tissues.

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5. Conclusion

We can conclude that topical oxygen therapy with blue®m products, according to clinical and scientific findings, can be considered novel oral care therapy in clinical practice. Further clinical investigations are required. The clinical recommendations as presented in this review are meant to help dentists maintain their patients' oral health. Most of suggestions and treatment protocol are supported by current evidence-based guidelines as well as the results of the relevant research. However, there are some areas where there isn't enough published research, so recommendations specific to conventional practice have been made based on the agreement of experts in the field. It is advised that the clinical guidelines as presented in this review can be followed while taking into account the oral health status of each patient, the overall treatment objective, the available resources, institutional policies, and other care options.

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