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Tooth-bleaching: Mechanism, Biological Aspects and Antioxidants

V Tamara Perchyonok[1] and Sias R Grobler[2]

[1]*VTPCHEM PTY LTD, Glenhuntly, 3163, Australia*
[2]*Oral and Dental Research Institute, Faculty of Dentistry, University of the Western Cape, Private Bag X1, Tygerberg 7505, Cape Town, South Africa*

***Corresponding author:** V Tamara Perchyonok, Vtpchem Pty Ltd, Glenhuntly, 3163, Australia, **E-mail:** tamaraperchyonok@gmail.com

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Introduction

Tooth discoloration varies in etiology, appearance, localization, severity, and adherence to tooth structure. It may be classified as intrinsic, extrinsic, and a combination of both [1].

Intrinsic discoloration is caused by incorporation of chromatogenic material into dentin and enamel during odontogenesis or after eruption. Exposure to high levels of fluoride, tetracycline administration, inherited developmental disorders, and trauma to the developing tooth may result in pre-eruptive discoloration. After eruption of the tooth, aging, pulp necrosis, and iatrogenesis are the main causes of intrinsic discoloration.

Coffee, tea, red wine, carrots, oranges, and tobacco give rise to extrinsic stain [2]. Wear of the tooth structure, deposition of secondary dentin due to aging [2] or as a consequence of pulpnecrosis, or as a consequence of pulp inflammation, and dentin sclerosis affect the light-transmitting properties of teeth, resulting in a gradual darkening of the teeth.

Scaling and polishing of the teeth remove many extrinsic stains. For more stubborn extrinsic discoloration and intrinsic stain, various bleaching techniques may be attempted.

Tooth bleaching can be performed externally, termed night guard vital bleaching or vital tooth bleaching, or intracoronally in root-filled teeth, called non-vital tooth bleaching. The aims of the present review article are to review critically the literature on the biological aspects of tooth bleaching, including efficacy and side-effects of such treatments.

History of Bleaching

Bleaching of discolored, pulpless teeth was first described in 1864 [3] and a variety of medicaments such as chloride, sodium hypochlorite, sodium perborate, and hydrogen peroxide has been used, alone, in combination, and with and without heat activation [4]. The "walking bleach" technique that was introduced in 1961 involved placement of a mixture of sodium perborate and water into the pulp chamber that was sealed off between the patient's visits to the clinician [5]. The method was later modified and water replaced by 30-35% hydrogen peroxide, to improve the whitening effect [6]. The observation that carbamide peroxide caused lightening of the teeth was made in the late 1960s by an orthodontist who had prescribed an antiseptic containing 10% carbamide peroxide to be used in a tray for the treatment of gingivitis [7]. The observation was communicated to other colleagues and must be regarded as the beginning of the night guard bleaching era. More than 20 years later, the method describing the use of 10% carbamide peroxide in a mouth guard to be worn overnight for lightening tooth color was published [8]. The mechanistic details of the 3 preferred bleaching methods are summarized in the Figure 1.

The pH of Tooth-Whitening Products

Despite various potential toxicological side effects [9-11], peroxides have been used for many years to treat periodontal diseases [12,13]. Peroxides, usually in the form of hydrogen peroxide or carbamide peroxide, are also the active ingredient in most tooth-whitening agents. The safety, effectiveness and various side effects of these products on the intraoral structures have been investigated, and some products have been accepted by the American Dental Association for whitening teeth [14-18).

However, some bleaching products have been reported to have a pH as low as 4.0, while others have been reported to have a pH of 7.5 [19]. It has been reported that the greater the peroxide concentration, the more acidic the pH of the bleaching product [20]. Some in-office bleaching products that contain 35% hydrogen peroxide may have a low pH.

Subjecting the teeth and oral tissues to a low or high pH for an extended period of time may cause adverse side effects. When the pH falls below 5.2, enamel demineralization [21] and root resorption have been reported [20,22]. Recent research to investigate the effects of pH on enamel suggests that low pH and high acid concentrations cause enamel erosion [23,24]. Interestingly, adding small amounts of calcium to acidic solutions may decrease enamel loss by up to 50% [24,25].

Genotoxicity and Carcinogenicity of Bleaching Agents

The genotoxicity of hydrogen peroxide and of tooth whiteners containing carbamide peroxide has been evaluated [26]. The consensus arising from these evaluations was that direct contact with hydrogen peroxide induced genotoxic effects in bacteria and cultured cells. When hydrogen peroxide was administered to bacteria or cultured cells in the presence of catalase or other metabolizing enzymes, the effect

(1) $Na_2[B_2(O_2)_2(OH)_4]+2H_2O \rightarrow 2NaBO_3+2H_2O_2$

(2) $H_2NCONH_2 \bullet H2O_2 \longrightarrow H_2NCONH_2+H_2O_2$

(3a) $H_2O_2 \rightarrow 2HO^{\bullet}$
$HO^{\bullet}+H_2O_2 \rightarrow H_2O+HO_2^{\bullet}$
$HO_2^{\bullet} \leftrightarrow H^+ + O_2^{\bullet -}$

(3b) $2H_2O_2 \leftrightarrow 2H_2O+2\{O\} \leftrightarrow 2H_2O+O_2$

(3c) $H_2O_2 \leftrightarrow H^+ + HOO^-$

Figure 1: The formation of hydrogen peroxide from sodium perborate (Eq. 1) (Hägg G [91]) and from carbamide peroxide (Eq. 2) (Budavari et al. [92]). Hydrogen peroxide forms free radicals like hydroxyl and perhydroxyl radicals, and superoxide anions (Eq. 3a)(Gregus and Klaassen, 1995), reactive oxygen molecules that are unstable and transformed to oxygen (Eq. 3b) and hydrogen peroxide anions (Eq. 3c) (Cotton FA, Wilkinson G [93]).

was reduced or abolished. Testing of hydrogen peroxide for systemic genotoxic effects in animals revealed no evidence of *in vivo* mutagenicity. Since hydroxy radicals perhydroxyl ions, and superoxide anions formed from hydro-gen peroxide are capable of attacking DNA, the genotoxic potential of hydrogen peroxide is dependent on the accessibility of free radicals to target DNA. This may explain why hydrogen peroxide induces genotoxicity in the presence of metabolizing enzymes neither *in vitro* nor *in vivo*. Tooth whiteners containing carbamide peroxide were mutagenic in certain bacterial strains and non-mutagenic in the presence of additional activating enzymes. Several *in vivo* studies addressing the formation of micronuclei in bone marrow cells and sister chromatide exchange after exposure to carbamide-peroxide-containing products revealed no genotoxic effects.

Based on the aforementioned studies, hydrogen peroxide was shown to have a weak local carcinogenic-inducing potential. The mechanism is unclear, but a genotoxic action cannot be excluded, since free radicals formed from hydrogen peroxide are capable of attacking DNA. Several studies of DMBA carcinogenesis in mice skin and hamster cheek pouch indicate thathydrogen peroxide may act as a tumor-promoter [10,27]. The International Agency for Research on Cancer (IARC) concluded that there is limited evidence in experimental animals and inadequate evidence in humans for the carcinogenicity of hydrogen peroxide and classified the chemical into Group 3: Unclassifiable as to carcinogenicity to humans [28]. It appears unlikely that oral health products containing or releasing hydrogen peroxide up to 3.6% H_2O_2 will enhance cancer risk in individuals except in those who have an increased risk of oral cancer due to tobacco use, alcohol abuse, or genetic pre-disposition [29]. To evaluate higher concentrations of hydrogen peroxide was not the task of the committee.

Free Radical Formation, Antioxidants and Relevance in Health:

Generation of free radicals in living systems

The formation of free radicals can be from endogenous or exogenous origin. Endogenous free radicals are continuously produced during the normal metabolic processes in the body's normal use of oxygen, an element indispensable for life. The most important of these by-products consists of reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that result from the cellular redox process [30]. During cell respiration, oxidative phosphorylation takes place in the electron transport chain during which most of the oxygen is consumed. During the process, energy is trapped in the form of ATP and oxygen is converted to water. However, during incomplete reduction of O_2 by a single electron addition, the superoxide radical $O_2^{\bullet -}$ is formed [31]. Superoxide is regarded as the primary ROS, and once formed this highly reactive species can start several enzymatic reactions responsible for the formation of different ROS such as H_2O_2, the highly reactive hydroxyl radical $(OH^{\bullet})^-$, as well as reactive nitrogen species (RNS) such as nitric oxide ($NO^{\bullet}$), peroxynitrite ($ONOO^-$) and hypochlorous acid (HOCl) [32]. Nitric oxide is a RNS produced by enzymes which metabolise arginine, and is used as signaling molecules in a number of physiological processes such as neurotransmission, blood pressure regulation, defence mechanisms, smooth muscle relaxation and immune regulation [32]. Exogenous origins of free radicals include heat, trauma, ultrasound, ultraviolet light, ozone, smoking, exhaust fumes, radiation, dental materials, infection, excessive exercise and therapeutic drugs [33].

Antioxidants

Antioxidants are substances that are able to reduce the free radical concentrations in cells and the body. They also react at different stages of the free radical formation. They can be preventive, such as superoxide dismutase or interceptive, such as vitamin C. Furthermore; the antioxidant defense systems of the human body can be classified into two groups, the enzymatic- and the non-enzymatic defence system. Most of the antioxidants present in the cell such as superoxide dismutase, glutathione peroxidase, catalase, glutathione reductase and thioredoxin are endogenous enzymatic systems, and produced within the cell [34]. Superoxide dismutase is an important endogenous antioxidant, and the first line of defence against free radicals. It converts superoxide radicals to H_2O_2. Then, the glutathione peroxidase and the catalase present in the cytoplasm of the cells will remove the H_2O_2 produced by reducing it to H_2O [35].

Vitamin E and vitamin C, together with other exogenous chemicals such as carotenoids and flavonoids, are essential nutrients and non-enzymatic antioxidant scavengers obtained from the normal human diet [36]. They mostly act as an interceptive radical chain, breaking reactions by trapping peroxyl and other reactive radicals [35].

Non-enzymatic antioxidants can also be metabolic antioxidants. Metabolic antioxidants are the endogenous antioxidants produced by metabolism in the body and include lipoid acid, glutathione, L-ariginine, co-enzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, etc [35].

Oxidative stress

Although the harmful effects of free radicals in biological systems were discovered about half a century ago, the importance of free radicals and antioxidants, and the therapeutic potential of the latter in health and disease, only became clear in recent years [35]. Usually, low or moderate concentrations of ROS and RNS form part of the development process of cellular structures, and the host cellular defense mechanisms such as the phagocytic destruction of bacteria [35]. Normally, there is a balance between the formation and removal of these free radicals. However, when this balance is shifted towards overproduction of free radicals or the removal of free radicals is diminished as a result of a shortage of antioxidants, oxidative stress develops. Because these free radicals have an affinity for nucleic acids, proteins and lipids, they play a pivotal role under conditions of oxidative stress in the development of a number of chronic and degenerative diseases [35]. Recently, it has been claimed that oxidative stress in saliva may play an important role in the onset of periodontal diseases [35]. Furthermore the oxidative stress in patients with periodontal disease could lead to the development of cardiovascular disease [35].

Antioxidants counteract oxidative stress and thereby lower the risk of the chronic and degenerative diseases [35]. Human saliva is rich in antioxidants such as uric acid, albumin, vitamin C and enzymes, which can be used as biomarkers in the measurement of oxidative stress in the oral cavity [37]. Since oxidative stress in the oral cavity can also be linked to certain systemic diseases [38] measurement of these biomarkers in saliva may provide an accurate indicator of oxidative stress in the body [38].

Advantages of Free Radicals in the Cell

Although free radicals can be very harmful to the body, they are also vital to human life. At low concentrations they are essential for normal physiological functions where they help to maintain homeostasis at the cellular level and play an important role as signaling molecules. Some of the important physiological functions include the generation of ATP used for energy transfer during oxidative phosphorylation, phagocytic destruction of invading pathogens, the killing of cancer cells by cytotoxic lymphocytes, apoptosis of defective cells, redox regulated production of NO used in the regulation of vascular tone, redox regulation of cell adhesion and other regulatory functions [37].

Oral Diseases, Oxidative Stress and the Role of Antioxidant Defenses in the Oral Cavity

The oral cavity is lined with delicate mucus membranes that allow rapidabsorption of harmful chemicals present in food, drinks, tobacco products and dental materials across its surface. The oral tissues are also vulnerable to cell damage through trauma, bacterial onslaught and other disease-causing agents. The oral cavity is therefore, uniquely susceptible to oxidative stress that can be responsible for a number of oral diseases such as periodontitis [37], aphthous ulcers [37,38] lichen planus [38] and oral sub-mucous fibrosis [39] some of which may develop into oral cancers [40].

Oral lesions, whether they are infected or not, will always trigger immune responses. During the resulting inflammatory processes, there is usually an over-production of ROS by the leukocytes promoting cytotoxicity, and this may initiate and/or amplify inflammation [41,42]. The ROS and RNS produced may initiate free radical chain reactions, which mediate tissue damage through DNA damage, lipid peroxidation, protein damage, oxidation of antiprotease and the stimulation of pro-inflammatory cytokine release [33]. Periodontitis, one of the most common oral infections induced by bacteria and bacterial products and characterized by inflammatory destruction of tooth supporting connective tissues and alveolar bone, is a good example of this process [41,42].

Antioxidants can remove the harmful effects of these free radicals. Saliva is a natural defence against bacteria and other substances pernicious to the oral cavity, and the antioxidants present in saliva are among the most important elements that aid in protection against these diseases. Antioxidants present in saliva include uric acid, albumin, ascorbic acid, glutathione and enzymes such as transferrin, lactoferrin and ceruloplasmin [43]. While uric acid is the main antioxidant present at high concentrations in saliva, the role of melatonin as a potent antioxidant, and its role during oxidative stress in the oral cavity, became of importance recently [44,45]. Melatonin is formed in the pineal gland and discharged in blood from where it is released into the saliva via the salivary glands. Melatonin has strong antioxidant potential and immunomodulatory, anti-inflammatory, and anticancer properties. Melatonin may interfere in the function of osteoclasts and thereby inhibit bone resorption as a result of periodontal disease and dental implants. In addition, melatonin decreases cytotoxic and genotoxic effects of methacrylate monomers used in dental materials [44,45].

Adverse Effects of Bleaching

Effect of bleaching and hydrogen peroxide on pulp

Studies have been conducted to examine the penetration of hydrogen peroxide and carbamide peroxide into the pulp chambers of teeth. Human and canine studies showed that both low (10%) and high (35%) concentrations of bleaching agents readily penetrate the pulp chamber [46-49]. Cohen applied 35% hydrogen peroxide and heat for 30-minute sessions to human teeth due to be removed for orthodontic treatment [47]. Varying degrees of sensitivity, lasting from 24–48 hours, were reported by 78% of the subjects. Histological findings in both the experimental and control groups showed that, except for moderate vasodilation and aspiration of odontoblast nuclei into the dental tubules, all pulps were normal. There were no histological findings to explain the sensitivity experienced by the subjects. A possible explanation may be that pressure builds in the pulp chamber as a result of the heat applied, causing the sensation of pain. The sensitivity, moderate vasodilation and aspiration of odontoblasts into the dental tubules appeared to be reversible in most cases [46-49].

Although clinical observations and scientific literature report short-term, minimal hypersensitivity to in-office and at-home bleaching treatments, there have been studies published that raise concerns about possible harmful effects of some bleaching agents on the pulp [50-54]. Glucose metabolism and protein synthesis, especially collagen synthesis, are the two most central metabolic processes occurring in the pulp. These metabolic reactions are catalyzed by enzymes that are sensitive to changes in environmental conditions [54]. Bowles and Thompson examined combined effects of heat and hydrogen peroxide on pulpal enzymes and found that most of the enzymes were relatively resistant to the effects of heat up to 50°C [52]. However, nearly every enzyme tested was inhibited to some degree by hydrogen peroxide. At concentrations as low as 5% some enzymes were completely inactivated. Results indicated that a combination of heat and hydrogen peroxide might increase the permeability of the pulp and potentiate the effects of hydrogen peroxide on the pulp. While the pulp appears to be quite resilient, there is concern for patients who may apply bleaching agents for longer periods of time or more frequently than recommended in order to hasten the achievement of whiter teeth. The long-term effects of frequent or prolonged use of bleaching agents on pulps are unknown [51-54]. The reasons for tooth sensitivity during vital tooth bleaching are not clear. Studies are inconclusive regarding the pulpal considerations of vital tooth bleaching. What is clear, however, is that case selection is critical. Considerations prior to initiating tooth whitening procedures should include assessment of the condition of existing restorations, cervical erosion, enamel cracks, and the estimated duration and repetition of bleaching required to obtain and maintain the desired effect [55].

Adverse effects on hard tooth surfaces

Cervical root resorption is an inflammatory-mediated external resorption of the root, which can be seen after trauma and following intracoronal bleaching [56].

A high concentration of hydrogen peroxide in combination with heating seemed to promote cervical root resorption [56,57], in line with observations made in animal experiments [58-60]. The underlying mechanism for this effect is unclear, but it has been suggested that the bleaching agent reaches the periodontal tissue through the dentinal tubules and initiates an inflammatory reaction [61]. It has also been speculated that the peroxide, by diffusing through the dentinal tubules, denatures the dentin, which then becomes an immunologically different tissue and is attacked as a foreign body [62]. Frequently, the resorption was diagnosed several years after the bleaching [56,62]. *In vitro* studies using extracted teeth showed that hydrogen peroxide placed in the pulp chamber penetrated the dentin [63] and that heat increased the penetration [64]. The penetration has been found, *in vitro*, to be higher in teeth with cervical defects of the cementum [64,65], and that may enhance the effects of hydrogen peroxide following repeated exposures. Based on the cited literature, the use of a thermo-catalytic bleaching procedure in teeth with cervical defects of the cementum constitutes a risk factor for the development of cervical resorption. In addition, efficacy studies have shown that 30% hydrogen peroxide was not essential to the attainment of an acceptable treatment outcome.

Tooth crown fracture has also been observed after intra-coronal bleaching [66] most probably due to extensive removal of the intra-coronal dentin. In addition, intra-coronal bleaching with 30% hydrogen peroxide has been found to reduce the micro-hardness of dentin and enamel [67] and weaken the mechanical properties of the dentin [68].

Local side-effects

Tooth sensitivity is a common side-effect of external tooth bleaching [69]. Tooth sensitivity normally persists for up to 4 days after the cessation of bleaching treatment [47,69,70].

The mechanisms that would account for the tooth sensitivity after external tooth bleaching have not yet been fully established. *In vitro* experiments have shown that peroxide penetrated enamel and dentin and entered the pulp chamber [71] and that the penetration of restored teeth was higher than that of intact teeth [72]. The amount of peroxide detected in the pulp chamber was related to the concentration of hydrogen peroxide in the preparations applied [72], and also varied among different brands of bleaching agents with the same declared concentration of carbamide peroxide [71]. The concentration of peroxide in the pulp chamber was not determined in the above studies, and the clinical significance of the findings is therefore unclear [73].

Tooth sensitivity was also a common symptom in patients who had not bleached their teeth, and their symptom was correlated with gingival recession [74]. Patients with a previous history of tooth sensitivity may thus have a higher risk for such an adverse effect from external tooth bleaching, and this should be taken into account before treatment begins.

Mucosal irritation

A high concentration of hydrogen peroxide (from 30 to 35%) is caustic to mucous membranes and may cause burns and bleaching of the gingiva. In animal experiments, exposure of the gingiva to 1% H_2O_2 for 6 to 48 hrs resulted in epithelial damage and acute inflammation in the sub-epithelial connective tissue [75]. It is therefore advisable that the tray be designed to prevent gingival exposure by the use of a firm tray that has contact with solely the teeth. In this respect, the newly introduced bleaching strips may be unfavourable, since the bleaching gel will come into contact with the gingiva.

Alteration of enamel surface

Morphological alteration of the enamel following tooth bleaching has been addressed in several *in vitro* studies [76]. Compared with the untreated control surfaces, the enamel surface exposed to the bleaching agents underwent slight morphologic alterations [77]. A high concentration of carbamide peroxide was detrimental to enamel surface integrity, but the damage was less than that seen after phosphoric acid etch [78]. A clinical implication of these findings may be that the teeth are more susceptible to extrinsic discoloration after bleaching due to increased surface roughness.

Effects on restorations

Data from laboratory studies documented increased mercury release from dental amalgams exposed to carbamide peroxide solutions for periods ranging from 8 hrs to 14-28 days [79,80]. The amount of mercury released varied with type of amalgam and type of bleaching agent and ranged from 4 times to 30 times higher than in saline controls. It has been suggested that bleaching may increase the solubility of glass-ionomer and other cements [81]. Furthermore, the bond strength between enamel and resin-based fillings was reduced in the first 24 hrs after bleaching [82]. After 24 hrs, there was no difference in the strengths of dental composite resin cement bonds to bleached and non-bleached enamel [83].

Following bleaching, hydrogen peroxide residuals in the enamel inhibit the polymerization of resin-based materials and thus reduce bond strength [62]. Therefore, tooth-bleaching agents should not be used prior to restorative treatment with resin-based materials.

To minimize this inconvenience, the treatment of the whitened dental structure with antioxidants has been recommended, for example, with sodium ascorbate (10%), to enable the completion of aesthetic restorations in shorter periods, as sodium ascorbate removes residual oxygen and promotes higher adhesiveness to the whitened dental substrate [75,84].

Antioxidants derived from ascorbic acid are used for decreasing the time interval between dental whitening and definitive restoration, thus enabling for the restoration procedure to be made with the prospect of maintaining longevity and durability of the adhesive [85]. However, application time of antioxidants for reverting the adverse effects on adhesion to the enamel and the dentine [86] has not been considered as entirely feasible yet, as it is seen as too lengthy for clinical uses.

Several methods have been proposed to decrease micro leakage due to bleaching, including removal of the superficial enamel layer, pre-treatment of the bleached enamel with alcohol, use of adhesives containing organic solvents, cleansing of the cavity with antioxidants, and a post-bleaching period ranging from 24 h to 3 weeks [87]. It has been shown that removal of the superficial enamel layer is ineffective because bonding weakens both superficially and internally [84].

Several antioxidant agents have been introduced, such as sodium ascorbate, ascorbic acid, butylhydroxyanisole, catalase, ethanol, acetone, glutathione, peroxide, α-tocopherol, and sodium bicarbonate, in order to better control restoration micro leakage [84]; however, only a few of them were found to be effective. Recently, a biocompatible and neutral antioxidant, 10% sodium ascorbate, was shown to be able to remove the residual peroxide and oxygen, so that compromised bonding to bleached tooth structures, such as dentin or enamel, could be reversed [88].

Furthermore, Moosavi et al. (84) demonstrated that the addition of surfactant (0.2% Tween® 80) to a sodium ascorbate formulation could significantly reduce the micro leakage after nonvital bleaching. Only one study [89] has investigated the use of catalase in improving the composite–resin bond strength after tooth bleaching. In another study [90], it was reported that catalase could be used as an adjunct to effectively eliminate residual hydrogen peroxide from the pulp chamber and the surrounding periodontal tissues following intra-coronal bleaching of non-vital teeth. In the present study, we examine the effect of catalase on improving adhesion between composite resin and externally bleached teeth and on reduction of micro leakage after external tooth bleaching.

Overt signs of hydrogen peroxide toxicity in dental tooth whitening have not been recognized and researchers have yet to definitively determine the long term effects of hydrogen peroxide when used in tooth bleaching agents.

Conclusion

What is evident from a review of the literature is the lack of consensus in much of the research. Many areas of concern have not yet been thoroughly investigated. It is well-documented that teeth can be bleached. Most authors conclude that retreatment is necessary but disagree on the intervals of time between treatments with reports ranging from one to three years. Transient clinical side-effects such as thermal sensitivity and mucosal irritation have been reported. Bleaching agents exert some changes in hard and soft oral tissues and in restorative materials, although it is uncertain if these changes are clinically significant. The short-term effects on dental hard tissues and pulpal tissues appear to be reversible. Questions about the frequent and/or long-term use of bleaching agents and their impact on dental hard tissues, pulpal tissues and oral soft tissues remain. Hydrogen peroxide agents pose some health risk concerns when used in biological systems. The impact of hydrogen peroxide on human oral mucosal antioxidant defense mechanisms is not yet completely understood. Long-term scientific human studies are needed. Because dental tooth whitening is likely to continue to be an available treatment option, dental hygienists can use the current literature to educate the public about the pros and cons of tooth whitening agents and procedures. When bleaching procedures are to be implemented, dental hygienists can ensure that the client is a non-smoker with healthy periodontium, has no cervical erosion or enamel cracks, and has intact restoration margins. Clients should be provided with custom-fitted bleaching trays with viscous

bleaching gel and be advised to follow instructions very carefully. Clients should be firmly reminded not to retain the trays with bleaching agent in their mouths overnight while sleeping, nor to increase the amount of bleaching agent or the frequency of their use of bleaching agents without first consulting a dental professional.

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