VERIFIABLE CPD PAPER

IN BRIEF

- Provides a review of current safety issues and adverse effects of hydrogen peroxide tooth whitening.
- Helps the reader recognise and understand any potential problems with the use of hydrogen peroxide tooth whitening agents.
- Critically reviews the available literature on safety issues and adverse effects of hydrogen peroxide tooth whitening.
- Outlines some simple guidelines based on the available literature for use to the reader when carrying out hydrogen peroxide tooth whitening.

Hydrogen peroxide tooth-whitening (bleaching) products: Review of adverse effects and safety issues

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Hydrogen peroxide in the form of carbamide peroxide is widely used for tooth whitening (bleaching), both in professionally- and in self-administered products. Adverse effects have become evident. Cervical root resorption is a possible consequence of internal bleaching and is more frequently observed in teeth treated with the thermo-catalytic procedure. Tooth sensitivity is experienced in 15-78% of patients undergoing external tooth bleaching. However, clinical studies addressing other adverse effects are lacking. Direct contact with hydrogen peroxide induces genotoxic effects in bacteria and cultured epithelial cells, but the effect is reduced or totally abolished in the presence of metabolising enzymes. Several carcinogenesis studies, including the hamster cheek pouch model, indicate that hydrogen peroxide (H_2O_2) might possibly act as a promoter. Until further clinical research is concluded to address the question of possible carcinogenicity, it is recommended that: tooth-bleaching products using concentrated H_2O_2 should not be used without gingival protection; that H_2O_2 containing products should be avoided in patients with damaged or diseased soft tissues. For nightguard vital bleaching, minimal amounts of low dose H_2O_2 (including in the form of carbamide peroxide) are preferred, thereby avoiding prolonged and concentrated exposures.

INTRODUCTION

Contemporary tooth whitening (tooth bleaching) systems are based primarily on hydrogen peroxide (H_2O_2) or one of its precursors, carbamide peroxide. These bleach the chromogens within the dentine, thereby reducing the body colour of the tooth and are often used in combination with an activating agent such as heat and/or light. Such agents can be applied externally to the teeth (vital bleaching) or internally within the pulp chamber (non-vital bleaching).

Case reports and small clinical studies have confirmed that predictable tooth whitening can be achieved using a 10% carbamide peroxide gel in a bleaching tray at night, (the nightguard vital bleaching technique),[1-9] H_2O_2 strips[10] and 'power bleaching' using 35% H_2O_2 with or without light and/or heat activation.[11,12] The 'walking bleach' technique introduced in 1961 for the bleaching of non-vital teeth involved sealing a mixture of sodium perborate and water into the pulp chamber between patients' visits.[13] The method was later modified and water replaced by 30-35% H_2O_2, to improve the whitening effect.[14]

Concerns have been expressed over the potential adverse effects of the use of H_2O_2 tooth whitening agents. The adverse effects that have been reported in cellular, animal and human studies include: cervical root resorption associated with non-vital bleaching; increased tooth sensitivity associated with vital bleaching; alteration in the surface topography of enamel; reduction in bond strength of resin based materials and the possibility that H_2O_2 may have carcinogenic or tumour promoting capabilities.

It is the purpose of this paper to review the available information on the side effects and safety of H_2O_2 in tooth whitening.

Hydrogen peroxide

Hydrogen peroxide (H_2O_2) is a colourless liquid with a bitter taste and is highly soluble in water to give an acidic solution. H_2O_2 is an oxidising agent with a wide number of industrial applications in for example, bleaching or deodorising textiles, wood pulp, hair, fur and foods, in the treatment of water and sewage, as a seed disinfectant and neutralising agent in wine distillation. Low concentrations of H_2O_2 have been found in rain and surface water, in human and plant

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tissues, in foods and beverages and in bacteria.[15]

Chemical reactions of hydrogen peroxide

Hydrogen peroxide is a reactive oxygen species, along with superoxide (O2-), hydroxyl (HO), peroxyl (ROO) and alkoxyl (RO).[16] In human tissue, intrinsic sources of H_2O_2 are organelles (especially mitochondria), salivary cells, microorganisms and the lungs.[17] Hydrogen peroxide production can be followed by the liberation of highly reactive oxygen species in the body via enzymatic and spontaneous redox reactions that often involve interaction with transitional metals such as iron or copper.

Enzymes such as catalase, glutathione peroxidase and superoxide dismutase catalyse the decomposition of H_2O_2 into water and oxygen.

Reactive oxygen radicals are a potential source of cell damage through causing DNA strand breaks, genotoxicity, and cytotoxicity, but these radicals tend neither to cross biological membranes nor travel large distances within a cell. Antioxidants provide a source of electrons that reduce hydroxyl radicals to water.

However, when exogenous H_2O_2 levels overwhelm cellular protective mechanisms, H_2O_2 presents a health hazard.[15,18] Individuals with acatalasia lack catalase activity, leading to high endogenous H_2O_2 levels causing necrosis and ulceration of soft and hard tissues.[19]

Hydrogen peroxide toxicity

Thirty per cent H_2O_2 can cause severe irritation or burns on contact with skin or eyes.[16] Following inadvertent irrigation of H_2O_2 into the periodontal ligament during root canal treatment, contact of the H_2O_2 with blood and tissue proteins produces effervescence, liberating oxygen and causing tissue emphysema.[20]

Following application of 30% H_2O_2 at 15 minute intervals (four applications) to the tip of rat tongue, oedema was followed by intraepithelial and some subepithelial vesiculation, changes preventable by prior administration of catalase.[21]

Prolonged application of a dilute 0.3 molar H_2O_2 solution onto the ventral tongue of dogs similarly resulted in oedema.[22] Gingival tissues of dogs respond similarly to a continuous application of 1% H_2O_2 solution over 48 hours – oedema, followed by epithelial vacuolisation and finally destruction and sloughing of the cornified layer. A cellular response similar to that in acute inflammation occurred. Increase in vascular permeability is likely, as there is severe oedema, a large number of acute inflammatory cells, haemoconcentration in blood vessels and presence of fibrin strands. After 48 hours there was no cellular evidence of a chronic reaction replacing the acute reaction.[23]

Hydrogen peroxide mouth rinses can be responsible for objective and subjective adverse effects including mouth irritation and discomfort, dryness, loss of taste, elongation of filiform papillae and diffuse mucosal whitening.[24] There are also changes in epithelial proliferation rate and morphological changes with epithelial thickening but fewer epithelial ridges. The PCNA (proliferating cell nuclear antigen) index, an indication of cell proliferation, increases in basal and parabasal layers of epithelium.[25] At baseline, although smokers had a significantly higher PCNA index than non-smokers, this difference disappeared following bleaching indicating stimulation of cell division activity by peroxide similar to that produced by smoke. In view of this, the workers concluded that 10% carbamide peroxide could act as a tumour promoter in the presence of mutated cells.[25]

Weekly (for four weeks) 20 minutes applications of 10% carbamide peroxide onto the dorsal tongue of rats also increased basal layer PCNA expression, but this is only transitory, with increased PCNA expression evident only on day 0 after the last application and not on day 10 or 20. Of note were that no mucosal alterations were detected.[26]

At a cellular level, Schraufstatter *et al.* demonstrated hydrogen peroxide to induce poly-ADP-ribose polymerase activation followed by NAD depletion and a fall in ATP, resulting eventually in cell death.[27]

Dental pulp is reported to have a low peroxidase enzyme activity due to a sparse cell population of fibroblasts. Studies have reported the inhibition as well as inactivation of pulpal enzymes by H_2O_2. The quantity of peroxides penetrating the pulp chamber of extracted teeth exposed to peroxides is sufficient to produce toxic effects on cultured fibroblasts, and though there have been few reports of untoward pulpal responses, this suggests caution is warranted.[28]

Cervical root resorption after internal (non-vital) tooth bleaching.

Intracoronal bleaching requires healthy periodontal tissues and a root canal that is properly obturated to prevent the bleaching agent from reaching the periapical tissues.[29] *In vitro* studies have concluded that sodium perborate in water, sodium perborate in 3% and 30% hydrogen peroxide, and 10% carbamide peroxide are all efficient at internal bleaching of non-vital teeth.[30-34] Various heat sources may be applied to speed the reaction and improve the bleaching effect.[35] The medicament is sealed in the pulp chamber for three to seven days, and is thereafter replaced regularly until acceptable lightening is achieved.

An adverse effect that has been reported following internal tooth bleaching is cervical root resorption (an inflammatory-mediated external resorption of the root).[36] Table 1 summarises the available data to support a correlation between internal tooth bleaching and cervical root resorption. When interpreting the data in Table 1 it is important to note that there are a large number of cases that had suffered known trauma. In these cases it is very difficult to distinguish if the root resorption noted was due to the effect of the bleach or the trauma.

A high concentration of hydrogen peroxide in combination with heating seems to promote cervical root resorption.[29,36] The underlying mechanism for this effect

Table 1 Studies correlating internal tooth bleaching and cervical root resorption

Internal Bleaching Procedure	Type of study	Observation time	No. of Patients	No. of Teeth	Trauma	Cervical Resorption	Reference
H2O2 (a)	Case report			2	2	All teeth	43,44
NaBO3 + 30% H2O2	Case report			1	1	All teeth	45
NaBO3 + 30% H2O2 + Heat (b)	Case report			18	15	All teeth	37,46,47, 48,49
NaBO3 + 30% H2O2 (replaced once a week)	Follow up	3-15 years	20	112	No Known	0%	50
NaBO3 + oxygen-water	Follow up	4 years	31	248	No Known	0%	51
NaBO3 - replaced every 10-15 days	Follow up	3 years	86	95	91	0%	52
(a) + (b)	Follow up	1-8 years	46	58	22	6.9%	36

is unclear, but it has been suggested that the bleaching agent reaches the periodontal tissues through the dentinal tubules and initiates an inflammatory reaction.[37] *In vitro* studies using extracted teeth showed that hydrogen peroxide placed in the pulp chamber penetrated the dentine,[38] that heat increased the penetration[39] and that the penetration is greater in teeth with cervical cemental defects.[40]

Intracoronal bleaching with 30% hydrogen peroxide reduces the microhardness of dentine and enamel[41] and mechanically weakens the dentine.[42]

Increased sensitivity after external (vital) tooth bleaching

Vital tooth bleaching can be performed by 1. dentist-administered bleaching – the use of a high concentration of hydrogen peroxide (35-50%) or carbamide peroxide (35-40%), often supplemented with a heat source; 2. dentist-supervised bleaching – using a bleaching tray containing a high concentration of carbamide peroxide (35-40%) placed in the patient's mouth for 30 minutes to two hours in the dental office; 3. dentist-provided bleaching – known as 'at home' or 'nightguard' bleaching and administered by the patient applying 5-22% solution of carbamide peroxide in a custom-made tray; and 4. over-the-counter products, often based on carbamide peroxide or H_2O_2 of various concentrations and placed in a prefabricated tray or on strips, and adjusted by the user.

Case reports and small clinical studies have confirmed that a 10% carbamide peroxide gel used in a bleaching tray at night, (the so-called nightguard vital bleaching technique), produces predictable tooth whitening[1-9] as do H_2O_2 strips[10] and 'power bleaching' using 35% $H_2O_2$with or without light and/or heat activation.[11,12]

Tooth sensitivity is a common adverse effect of external tooth bleaching (Table 2).[53] Data from various studies of 10% carbamide peroxide indicate that from 15-65% of patients reported increased tooth sensitivity.[54-57] Higher incidences of tooth sensitivity (from 67-78%) were reported after bleaching with H_2O_2 in combination with heat.[58,59]

Tooth sensitivity normally persists for up to four days after bleaching,[58,60] but durations of up to 39 days have been reported.[56,57] In a clinical study that compared two different brands of 10% carbamide peroxide bleaching agent, 55% of the 64 patients reported tooth sensitivity and/or gingival irritation, and 20% of those who had experienced adverse-effects terminated the treatment because of discomfort.[56]

The mechanisms that could account for the tooth sensitivity after external tooth bleaching have not yet been fully established, but an *in vitro* experiment has shown that peroxide can penetrate enamel and dentine and enter the pulp chamber.[61]

Effect of bleaching on the structure of enamel

Significant surface alterations in enamel topography follow vital bleaching using carbamide or H_2O_2.[62,63] High concentrations of carbamide peroxide damage enamel surface integrity, but less so than phosphoric acid etch.[63] As a result of this increased surface roughness it is possible that teeth may be more susceptible to extrinsic discolouration after bleaching.

Table 2 Studies to support correlation between external tooth bleaching and cervical sensitivity

Type of Treatment	Bleaching rocedure	Duration of study	No. of patients	No. of controls	Incidence of sensitivity	Reference
In-surgery	30% H2O2 + heat, 3 visits of 30 min. during 3 weeks	30 days	19	0	78%	58
In-surgery	30% H2O2 + heat, 2-6 visits of 30 min.	No information given	15	0	67%	59
At-home	10% carbamide peroxide, 2 hrs or overnight	28 days	28	0	15%	60
At-home	10% carbamide peroxide overnight	14 days	24	0	64%	57
At-home	10% carbamide peroxide, day or night	6 weeks	37	0	38%	56
At-home	10% carbamide peroxide, 6-8 hrs/ day with solution changes	6 weeks	38	0	52%	56
At-home	10% carbamide peroxide, day + night or day with solution changes	6 weeks	27	0	78%	56

Effects of tooth bleaching on tooth restorations

Bleaching may increase the solubility of glass-ionomer and other cements[64] and reduce the bond strength between enamel and resin-based fillings in the first 24 hours,[65] but not later.[66] Following bleaching, H_2O_2 residues in the enamel may inhibit the polymerisation of resin-based materials and reduce bond strength.[67] Thus tooth-bleaching agents should not be used [for 24 hours] prior to treatment with resin-based materials.

Animal, cellular and bacterial studies relating to the safety of hydrogen peroxide

An extensive review of these has been undertaken by Naik *et al.* (2006).[68] The following provides a brief overview of this area.

Animal studies

In mice low doses of hydrogen peroxide (0.1% and 0.4%) administered in drinking water caused adenomas or adenocarcinomas in the duodenum.[69] These findings have been questioned and it has been proposed that the most likely cause of the lesions observed were the decreased water consumption of the mice and resultant abrasion of the luminal lining on ingestion of pelleted dry rodent food.[70,71] Another animal study by Weitzman *et al.* suggested that a known tobacco carcinogen 9, 10-dimethyl-1, 2-benzanthracene (DMBA) could be augmented in producing carcinogenesis in the buccal epithelium of hampsters by 3% H_2O_2.[72] These results have been disputed due to the small number of animals studied. Further studies in hampsters given up to 70mg/kg of H_2O_2 by oral intubation for up to six months[73,74] or up to 3% H_2O_2 in combination with DMBA applied five times daily for 16-20 weeks on the buccal epithelium[75] did not show any sign of carcinogenesis. Further studies on skin have concluded that H_2O_2 is inactive as a tumour promoter or carcinogen.[76,77]

Cellular studies

The response of mammalian cells to H_2O_2 is highly variable, dependent on factors such as catalase concentration and DNA repair activity. In one study, H_2O_2 induced a dose-dependent increase of hypoxanthine guanine phosphoribosyltransferase (HPRT) mutations *in vitro* in human T lympho-

cytes, most mutations being of the same kind as observed in T cells *in vivo*.[78] Another study, using human lymphocytes, assessing genotoxicity showed the main event induced by extracellular application of H_2O_2 to be necrosis and not micronucleus formation.[79]

In human cells, H_2O_2 acts synergistically with non hydrogen peroxide photoproducts to produce increased frequencies of chromosome aberrations and sister chromatid exchanges.[80,81]

However, with these studies there is a high potential for false positive results and the studies do not take into account absorption, distribution and excretion of the H_2O_2. Therefore genetic effects produced *in vitro* cannot be immediately transposed *in vivo*.

Bacterial studies

Bacteria lack distinct, membrane bound nuclei – their genetic material lies in the cytoplasm as a continuous loop of naked DNA and they would therefore be extremely vulnerable to H_2O_2. Abu-Shakra *et al.*[82] examined effects of H_2O_2 on salmonella strains, and found conflicting results. Mutagenicity appeared to be more a function of the strain genotype than the amount of catalase.[82] In any event, normal mammalian cells appear to have protective mechanisms able to eliminate the mutagenic response to H_2O_2 seen in bacteria.[83]

Clinical studies of hydrogen peroxide containing dental products

Mouthrinses

Hydrogen peroxide has been used as a mouthrinse for debriding oral wounds and producing a less favourable environment for anaerobic organisms.

Most often low dose H_2O_2 is used in mouthrinses, but in one study where 6% H_2O_2 was used to irrigate 122 patients with post-extraction pain, there were no reports of soft tissue irritation.[16]

When 1.5% H_2O_2 was used as a rinse for 18 months in orthodontic patients, no patients developed mucosal irritation.[84]

Similar results were noted in other studies, some even using combinations of hydrogen peroxide/povidone iodine or hydrogen peroxide/sodium chloride/sodium bicarbonate and iodine.[85,86]

Conversely, Branemark and Ekholm studying the effects of 3% H_2O_2 found increased injury to damaged tissue, thus delaying wound healing.[87] Rees and Orth confirmed these findings with two case reports where 3% H_2O_2 was used as a mouthrinse following prior tissue injury.[88]

Dentifrices

Dentifrices containing low dose H_2O_2 were shown to produce no soft tissue changes or irritation.[17] One study showed that decomposition of H_2O_2 in the dentifrice is enhanced six fold by the presence of baking soda. No substantial amount survived beyond brushing and after expectorating, very little material was present to interact with soft tissues in the oral cavity.[17]

Bleaching products

Numerous studies have observed the clinical effects of bleaching products containing H_2O_2 and carbamide peroxide. In a comparison of 6.5% H_2O_2 strips applied in total for 56 hours over eight weeks and 10% carbamide peroxide in a tray applied for 448 hours over the same period, significant whitening was noted with both systems in the maxillary teeth. However, in the mandibular teeth, the carbamide peroxide produced significantly more whitening compared with the H_2O_2 system. Both products produced a similar level of sensitivity and irritation, albeit the marked difference in application times.[89]

With carbamide peroxide, H_2O_2 and urea are produced. The degradation is slower than with H_2O_2 and the peroxide therefore remains in contact with tooth structure and tissues for longer. In one study measuring the degradation of 10% carbamide peroxide in bleaching trays, this was highest in the first hour and closest to the teeth. The possible reasons for this may be that H_2O_2 penetrates the tooth, reaction with the pellicle, oral fluids/stains on the teeth or with microorganisms which degrade the material. The active agent in carbamide peroxide is available in trays for more than 10 hours (10% remained by this time).[90]

The method of delivery can also have an effect on the peroxide released into the mouth. Comparing a 5% H_2O_2 strip with 10% carbamide peroxide in a tray both applied for 30 minutes on alternate days revealed that the peroxides in saliva are higher with the strips than the tray.[91]

Following the application of a 19% sodium percarbonate direct bleaching gel, the peak salivary H_2O_2 was 0.033% and peroxide levels had returned to baseline by 30 minutes.[92]

Measurements of salivary pH following use of 10% carbamide peroxide (pH5.3) in a guard revealed no significant reductions, rather the pH at times increased, possibly because the carbamide peroxide degrades into H_2O_2 and urea (and thus ammonia). Urea is also released from salivary glands and may have contributed to the increase in pH along with the increased salivary flow and buffering systems of saliva. It can be concluded that low doses of carbamide peroxide should not demineralise tooth structure.[93]

CONCLUSIONS

1. Cervical root resorption is a possible consequence of internal bleaching and is more frequently observed in teeth treated with a thermo-catalytic procedure.
2. Tooth sensitivity is a common side effect of external tooth bleaching.
3. Tooth-bleaching agents should not be used [for at least 24 hours] prior to restorative treatment with resin-based materials.
4. Urgent clinical studies are required on the genotoxic and tumour-promoting effects of hydrogen peroxide bleaching agents. Until such studies are available it is recommended that tooth-bleaching products using concentrated H_2O_2 should not be used without gingival protection to prevent exposure of the gingival tissues or mucosae. The use of H_2O_2 containing products should be avoided in patients with damaged or diseased tissues. For nightguard vital bleaching, minimal amounts of low dose H_2O_2 (10% carbamide peroxide) is preferred, avoiding prolonged and long-term use. Patients undergoing nightguard vital beaching should be regularly reviewed and monitored.

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