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Safety evaluation of a novel whitening gel, containing 6% hydrogen peroxide and a commercially available whitening gel containing 18% carbamide peroxide in an exaggerated use clinical study

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KEYWORDS

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Summary Objectives. The aim of this study was to compare the effect on oral soft tissue of a self-applied tooth whitening gel containing 6% hydrogen peroxide (Xtra White) with a marketed paint-on whitening gel containing 18% carbamide peroxide (Colgate Simply White) after 2-weeks of using products four times daily.

Methods. A 2-week, examiner-blind, stratified, parallel design clinical trial was conducted. Twenty subjects were divided into two groups, balanced according to age and gender. Subjects followed a 2-week, twice-daily regimen of brushing with standard fluoride toothpaste and applied gel product to facial aspects of six upper and six lower incisors/canines, twice in succession with 30 min between applications. Soft tissue examinations were performed on Day 1, before the first application of the test products, and on Day 2, 5, 8 and 15.

Results. During the 2-week treatment period, twelve adverse reactions were recorded as potentially attributable to the study products, evenly split between the two test groups. All reports were mild in symptoms and resolved without the need of medical intervention. None of the subjects experiencing an adverse event requested to be withdrawn from the study.

Conclusions. Under the exaggerated use conditions of this test, there was no evidence to suggest that either of the whitening gels produced irritation that was building or developing during the course of the study. It is concluded that both products are safe for their intended use.

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Introduction

Bright white healthy smiles are a global aspiration, which is reflected through increased sales of

tooth whitening toothpastes, gels, chewing gums, floss, strips and toothbrushes. Tooth discoloration can occur through a build up of extrinsic stains in the enamel pellicle in combination with the intrinsic tooth colour, determined by the underlying dentine layer.¹ Whiter teeth can be obtained through two routes: by using a whitening toothpaste containing abrasive systems to remove and reduce the build-up of extrinsic stains² or by using tooth whitening technologies such, as peroxides, to alter the intrinsic colour. For over 100 years, peroxides have been used to whiten teeth by permeating tooth enamel, causing pigments within the dentine/dentine-enamel junction to decolourise.³

Extensive toxicological studies have been published to examine the safety of hydrogen peroxide/carbamide peroxide for tooth whitening and conclude that 10% carbamide peroxide (equivalent to 3.6% hydrogen peroxide), when applied in a mouth tray (2 h/day for 14 days), is safe.⁴⁻⁷ Recently, tray-less systems have been introduced in the form of whitening strips (comprising 6% hydrogen peroxide, worn for 1 h/day for 14 days) and an 18% carbamide peroxide paint-on whitening gel (used 1 min daily for up to 3 weeks).^{8,9} Although, these new systems contain higher peroxide concentrations, the total contact times are significantly reduced. Therefore, the peroxide dose will probably be no greater than that delivered by tray systems, hence, no safety issues are expected.

The most common oral events experienced when using tooth whitening products are gingival irritation and tooth sensitivity. These events are usually mild in severity and often resolve themselves while continuing to use the whitening product. Tolerability of such side effects is believed to be dependent upon peroxide concentration versus contact time, these are important factors that significantly influence product design.

A new convenient self-applied whitening system has been developed (Xtra White[†]), which comprises a 6% hydrogen peroxide gel, applied using disposable cotton bud applicators. This gel is applied twice daily over a period of 2 weeks to whiten teeth. The study reported here followed an 'exaggerated use' type of protocol, as described by Slezak et al.¹⁰ to explore the potential of this new whitening gel to cause irritation to the oral hard and soft tissues versus a marketed 18% carbamide peroxide paint-on whitening gel (Colgate Simply White).

Materials and methods

Twenty subjects were recruited to participate in a 2 week, examiner-blind, stratified, parallel design clinical trial. An independent Ethics Committee reviewed the protocol. Subjects, who voluntarily consented to participate and signed a consent form, were of either gender, aged between 18 and 66 years, in good general health and had a desire to lighten their upper and lower anterior teeth. Women who were pregnant or nursing were not included. Subjects were required to have at least four upper anterior teeth (incisors/canines) and four lower incisors to which a whitening gel could be applied. Subjects were not included if they had orthodontic bands, self-reported tooth hypersensitivity, crowns/veneers or visible cosmetic restorations on the facial surfaces of their upper incisors/canines. Subjects with advanced periodontal disease on upper incisors, or undergoing professional treatment for periodontal disease; those who had been treated for periodontal disease within the last 6 months, or those who regularly used mouthrinses for the treatment/control of a periodontal condition were also not accepted. Finally, subjects with known allergies or sensitivities to toothpaste or tooth bleaching products did not participate in the study.

Subjects were stratified based on their gender and age and randomly assigned to one of two treatment groups. The '6% hydrogen peroxide gel' treatment group received two jars of 6% hydrogen peroxide gel and two boxes of 30 cotton bud applicators (Xtra White[†], Unilever Oral Care); a toothbrush; two tubes of standard silica fluoride toothpaste (1000 ppm fluoride) manufactured by Unilever Research and Development, UK. These subjects were instructed to apply the whitening gel to the facial aspects of their upper and lower incisors and canines, after normal brushing, in accordance with manufacturers instructions. Thirty minutes after the first application, they reapplied the whitening gel. This double application of whitening gel was to be repeated twice a day for 14 days.

Subjects in the '18% carbamide peroxide gel' treatment group received two bottles of commercially available 18% carbamide peroxide gel with an applicator brush fixed in the lid of the bottle (Colgate Simply White, Colgate Palmolive, Piscataway NJ, US); a toothbrush; two tubes of standard silica fluoride toothpaste (as before). These subjects were instructed to paint the whitening gel on to the facial aspects of their upper and lower incisors and canines, after normal brushing in

[†] Marketed as Signal/Mentadent/Pepsodent/Aim Xtra White.

accordance with manufacturers instructions. Thirty minutes after the first application, they reapplied the gel. This double application of gel was to be repeated twice a day for 14 days.

The clinical investigator performed soft tissue examinations on Day 1, before the first application of the test products, and on Days 2, 5 and 8, before the first application of the product on each day. The final soft tissue examination was performed on Day 15, after the final product applications on Day 14. Soft tissue examinations constituted examinations of the lips, labial mucosa, buccal mucosa, hard palate, soft palate, tonsillar region, tongue, floor of mouth, alveolar mucosa and gingiva for signs of reddening/inflammation, ulceration, white patches (e.g. resolving cheek bites) and desquamation/sloughing of mucosal tissues. All changes from baseline in soft/hard tissues and medications were recorded as adverse events. The severity of symptoms experienced were classified as either 'mild' (defined as an awareness of symptoms or signs, but easily tolerated); 'Moderate' (symptoms cause enough discomfort to interfere with usual activity) or 'severe' (symptoms results in an incapacity to work or do usual activity).

Results

Nineteen (out of twenty) subjects completed the entire study. One subject failed to attend two scheduled visits and was therefore withdrawn for non-compliance with study procedures. A summary of age and gender is displayed in [Table 1](#).

Twelve adverse events relating to the study test products were recorded either during the soft tissue examinations or reported separately. All reports were diagnosed as mild by the clinical investigator and did not necessitate the discontinuation of product use. All cases were resolved without the need of medical intervention and none of the subjects experiencing an adverse event requested to be withdrawn from the study. Nine of the twelve adverse events were reported in the first week and resolved by Day 15 of the study. The remaining three adverse events were reported in the second

week of the study and resolved within 5 days of the study finishing.

Of the twelve adverse events the most common symptom was oral irritation (e.g. reddening in proximity to the treated teeth). Six cases of oral irritation occurred in subjects using the 6% hydrogen peroxide gel and four cases in those subjects using the 18% carbamide peroxide gel. One subject in the 18% carbamide peroxide gel group developed an aphthous ulcer. There was only one report of tooth sensitivity and this occurred in the 18% carbamide peroxide gel group.

Discussion

The study was designed to examine the potential of two whitening gel products to cause soft tissue irritation and tooth sensitivity when used excessively. The results show that only mild irritation and a very low level of tooth sensitivity were experienced and that each gel product generated a similar level of adverse events. The mildness of the symptoms is reflected in the observation that none of the subjects experiencing an adverse event requested to be withdrawn from the study.

Nine of the twelve adverse events were reported during the first week and resolved by the end of the trial. The other three adverse events were reported in the second week and resolved within 5 days of the study finishing. This finding suggests that the level and intensity of irritation was not building during the course of the treatment phase and that the onset of events was not related to previous exposure.

Gerlach et al.¹¹ reported that 18% of subjects using hydrogen peroxide whitening strips experienced mild and transient tooth sensitivity and 17.1% experienced oral irritation. This level of tooth sensitivity is far higher than that experienced in this exaggerated use study, which is probably related to the type of exposure. The level of oral irritation experienced during exaggerated use was three times greater than that reported for normal use of whitening strips and this effect is most likely related to the increased frequency of application. Normal use of the 6% hydrogen peroxide whitening gel by 58 subjects showed a similar level of oral irritation when compared to normal use of whitening strips.

Slezak et al.¹⁰ reported that no adverse events were found among 15 subjects using the same 18% carbamide peroxide whitening gel in a similar exaggerated use trial.

Table 1 Demographic data for subjects completing study.

Group	Number of subjects		Age	
	Men	Women	Mean	Range
6% Hydrogen peroxide	3	7	44.6	33-66
18% Carbamide peroxide	3	7	34.9	18-48

Conclusions

Under the exaggerated use conditions of this test, there was no evidence to suggest that either of the whitening gels produced irritation that was building or developing during the course of the study. It is concluded that both products are safe for their intended use.

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