

IS H₂O₂ SAFE?

Evidence to date indicates that properly formulated peroxide sources are safe.



PEROXIDE

- Most Extensively researched whitening technology
- Short term & extended use trials
- Positive & negative controls
- Adults & children

**Safety of Vital Tooth Bleaching with 6% Hydrogen Peroxide Whitening Strips:
Evidence from 18 Clinical Trials**

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ABSTRACT

Objective: This research summarizes an extensive clinical trials database on 6% hydrogen peroxide strip-based tooth whitening systems in order to ascertain factors that contribute to clinical safety and tolerability.

Methods: Data from 18 different randomized clinical trials were included in the meta-analysis. This inclusive assessment combined only subjects who used the peroxide strips. Whitening strip control was 0% hydrogen peroxide bleaching gel. Treatment was twice daily for 10 minutes over a 2-week period. Safety and tolerability were assessed from clinical observations and adverse events. A logistic regression model was used to identify possible risk factors for both safety and tolerability. **Results:** The data included 111 patients (18.2% total) with complete safety data. Mild and transient tooth sensitivity (11.1%) and erosion (1.7%) represented the most common adverse events during treatment. Age was a significant ($p < 0.0001$) effect on the severity of tooth sensitivity, with older subjects reporting less tooth pain during treatment. Race and gender were not significant contributors. Other adverse events were rare, and mild, and were resolved during the period of active treatment. Over 97% of adverse events were considered to be "mild" in severity and only 2 subjects (0.6% of the population) discontinued treatment early due to an adverse event. **Conclusion:** This meta-analysis further confirms the clinical safety and tolerability of vital bleaching with 6% hydrogen peroxide strip-based systems.

OBJECTIVE

This research summarizes an extensive clinical trials database on 6% hydrogen peroxide strip-based tooth whitening systems in order to ascertain factors that contribute to clinical safety and tolerability.

RESULTS

The most common adverse event (AE) in the 18 clinical trials were:

- Tooth sensitivity reported by 11.6% of clinical subjects
- Tooth erosion, reported by 1.1% of subjects

Adverse Events by Risk Factor

- 97% of adverse events were of mild severity.
- Mild adverse events resolved during the period of active treatment or within 1-4 days after treatment was completed.
- Only 2 subjects (0.6%) stopped treatment because of an adverse event.

CONCLUSION

This meta-analysis further establishes the clinical safety and tolerability of vital bleaching with 6% hydrogen peroxide whitening strips (Crest Whitening Strips).

Mild transient tooth sensitivity (11.6%) and erosion (1.1%) were the most commonly reported adverse events with 6% hydrogen peroxide strips.

Demographic and Behavior Parameters

Sample Size	316
Age	18-63 (34)
Gender (Female)	258 (75%)
Ethnicity (Caucasian)	246 (77.5%)
Race	27 (8.5%)
Black	24 (7.5%)
Hispanic/Latino	24 (7.5%)
Caucasian/Asian	27 (8.5%)
Coffee Tea Use	274 (87%)

Safety Endpoints

Diagnosed Sensitivity and Oral Irritation Assessment

The assessment was conducted on questioning of subjects at each visit about the presence or absence of hypersensitivity and erosion/trauma in each clinic location.

Statistical methodology:

The present risk factors for tooth sensitivity and oral irritation were identified using a logistic regression model.

Adverse Events by Risk Factor

- Only age was identified as a factor that was statistically significantly associated with tooth sensitivity ($p < 0.0001$).
- A similar pattern of older clinical subjects reported tooth sensitivity than younger subjects.

CONCLUSION

This meta-analysis further establishes the clinical safety and tolerability of vital bleaching with 6% hydrogen peroxide whitening strips (Crest Whitening Strips).

Mild transient tooth sensitivity (11.6%) and erosion (1.1%) were the most commonly reported adverse events with 6% hydrogen peroxide strips.

Procter & Gamble

Research presented at the 61st General Session of the IADR, June 22-26, 2002

combination peroxide bleaching system (dentifrice/bleaching gel/strip), while the other involved 6% hydrogen peroxide whitening strips. Both products were used according to manufacturer's instructions. Tooth sensitivity and oral irritation were assessed by subject report and oral examination. Bleaching Tolerability Severe-Days (BTSD) were calculated using oral, severity and duration data to compare treatments. Results: A total of 20 subjects (18% of the sample) reported either oral irritation or tooth sensitivity some time during the treatment period, while 10 subjects (50%) had treatment-related oral irritation observed by the examiner at one of the 2 post-treatment visits. BTSD means (SD) were 0.22 (0.35) and 0.43 (0.45) for the strip and combination groups, respectively. Between-group comparisons using the non-parametric Wilcoxon rank-sum test showed the strip system to be significantly ($p < 0.046$) more tolerated than the combination system. Conclusions: The 6% whitening strip group exhibited a 34% reduction in tooth sensitivity and oral irritation, and statistically significant fewer severe-days compared to the combination dentifrice/gel/strip system.

OBJECTIVE

This study compares the clinical tolerability of a combination bleaching system relative to a marketed control.

MATERIALS AND METHODS

A two-week, randomized, parallel group, clinical trial was conducted involving two bleaching systems.

RESULTS

A total of 20 subjects (18% of the sample) reported either oral irritation or tooth sensitivity some time during the treatment period. A total of 10 subjects (50% of the sample) had treatment-related oral irritation observed by the examiner. Transient tooth sensitivity or oral irritation (reported or observed) were more common in the combination group, affecting 65% of the population relative to 45% in the whitening strip group. Eighteen percent of all events were "mild" in severity. The median number of days in which of possible or probable treatment-related AEs was 1 day in the whitening strip group and 4 days in the combination group. With respect to severity and duration, the median BTSD score for the combination group was 0.21, while the median BTSD score for the whitening strip group was 0.00. Between-group comparisons showed that bleaching strips were better tolerated overall. The bleaching tolerability severity-days scores for the two treatment groups were statistically different with a p -value of 0.0465.

Figure 1. Bleaching Tolerability Severe-Days Distribution

Table 1. Bleaching Tolerability Severe-Days Summary

Statistic	Crest Whitening Strips	Rembrandt Plus
Number of Subjects	20	21
Mean (SD) BTSD	0.22 (0.35)	0.43 (0.45)
Min - Median - Max BTSD	0 - 0 - 1.07	0 - 0.21 - 1.57
Exact Two-sided p -value	0.0465	

CONCLUSION

The 6% whitening strip group exhibited a 34% reduction in both sensitivity and oral irritation, and statistically significant fewer severe-days compared to the combination dentifrice/gel/strip system.

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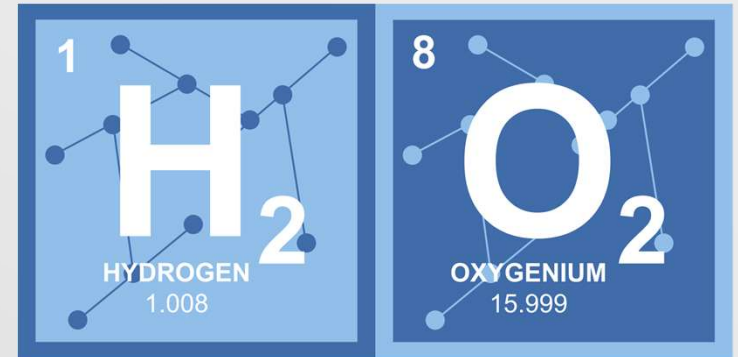
P&G Bibliography

of over 183 published papers and presentations on Whitening Products



PEROXIDE SAFETY AND THE SOFT TISSUE

1. Peroxide dissipates relatively fast on soft tissue
2. The amount of peroxide applied to the soft tissue is important for maintaining integrity (Vs concentration)



1. Walsh LJ. Safety issues relating to the use of H₂O₂ in dentistry. Aust Dent J. 2000 Dec;45(4):257-69.
2. Liochev SI. Reactive oxygen species and the free radical theory of aging. Free Radic Biol Med. 2013 Jul;60:1-4.
3. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 2006 Mar 10;160(1):1-40.
4. Davies MJ. Protein oxidation and peroxidation. Biochem J. 2016 Apr 1;473(7):805-25.
5. Staerck C, Gastebois A, Vandeputte P, Calenda A, Larcher G, Gillmann L, Papon N, Bouchara JP, Fleury MJJ. Microbial antioxidant defense enzymes. Microb Pathog. 2017 Sep;110:56-65.
6. Zhang YJ, Gan RY, Li S, Zhou Y, Li AN, Xu DP, Li HB. Antioxidant Phytochemicals for the Prevention and Treatment of Chronic Diseases. Molecules. 2015 Nov 27;20(12):21138-56.

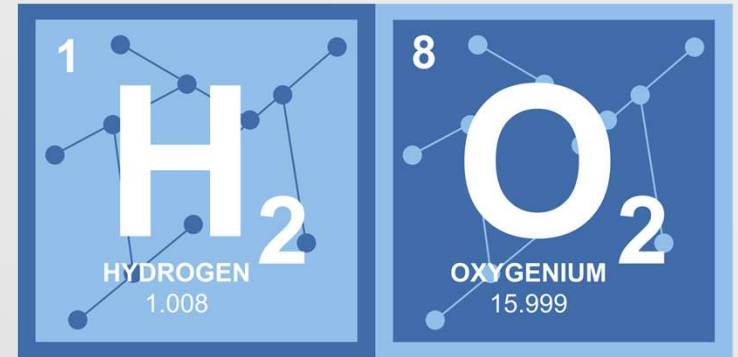


PEROXIDE SAFETY AND THE SOFT TISSUE

H_2O_2 is created by the human body's own immune systems as part of our protection against pathogens.

In the human body, immune system cells such as macrophages create H_2O_2 to help kill pathogens such as bacteria and viruses. If the body produces too much peroxide, our body's natural immunity produces an enzyme called catalase.¹⁻⁶

Catalase converts left over H_2O_2 into water and oxygen. The production of and elimination of H_2O_2 in our bodies is a normal function of our immune system



1. Walsh LJ. Safety issues relating to the use of H_2O_2 in dentistry. Aust Dent J. 2000 Dec;45(4):257-69.
2. Liochev SI. Reactive oxygen species and the free radical theory of aging. Free Radic Biol Med. 2013 Jul;60:1-4.
3. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 2006 Mar 10;160(1):1-40.
4. Davies MJ. Protein oxidation and peroxidation. Biochem J. 2016 Apr 1;473(7):805-25.
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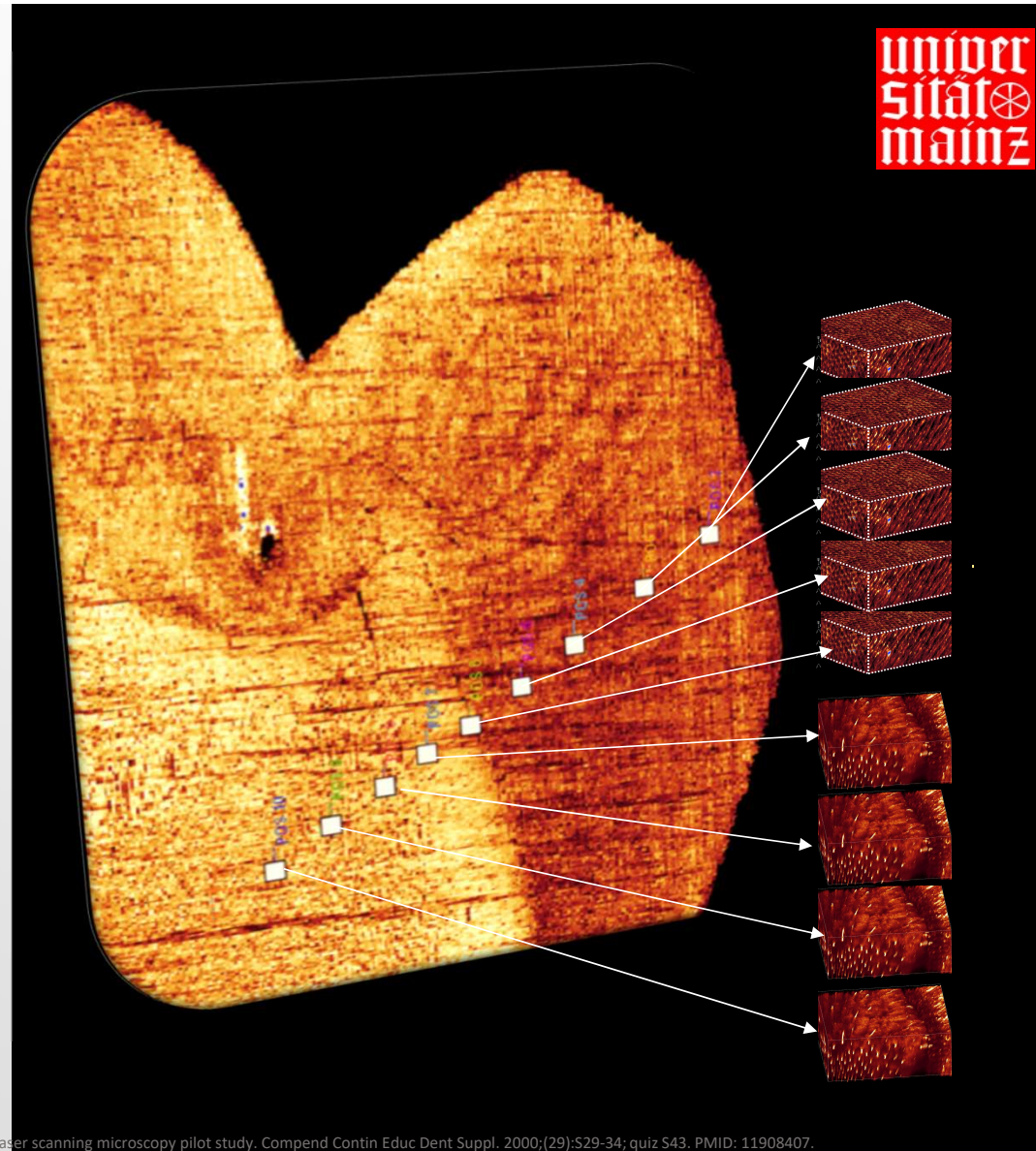


PEROXIDE SAFETY AND THE HARD TISSUE

Bleaching Does Not Alter Mineral Composition

Properly formulated peroxide sources do not damage enamel surfaces.

Peroxides also have no substantial effects on the structure, ultrastructure, physical properties or chemical composition of surface enamel, subsurface enamel or (bleached) coronal dentin.





PEROXIDE SAFETY AND THE ENAMEL

Abrasion

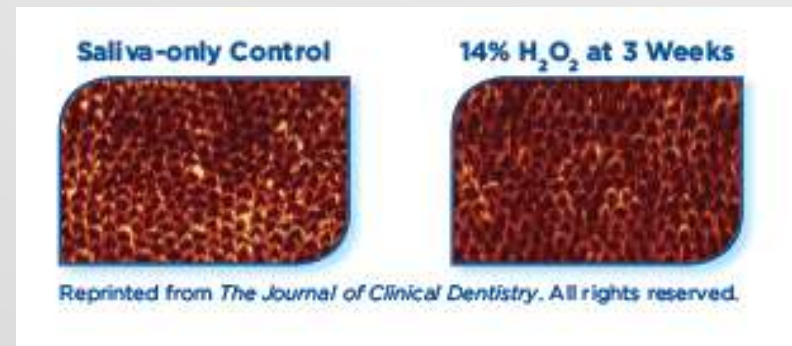
Peroxide treatment has no effects on abrasion susceptibility of enamel or root dentin

Caries

Peroxide treatment has no effects on enamel caries susceptibility

Erosion

Peroxide treatment has no effects on enamel or dentin erosion susceptibility





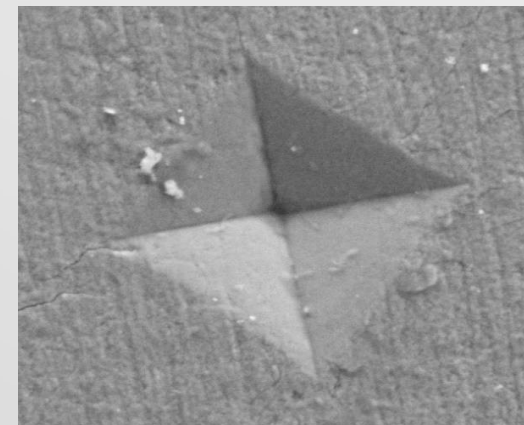
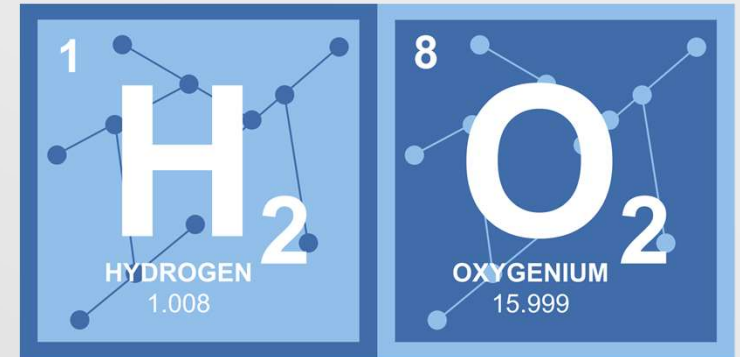
PEROXIDE SAFETY AND THE HARD TISSUE ¹⁻³

Crack Propagation analysis of teeth confirms whitening, even over whitening does not increase fracture susceptibility

Microscopy analysis reveal that whitening does not etch surface enamel of teeth

Whitening does not soften subsurface enamel

Whitening does not soften coronal subsurface dentin



Vickers Enamel Microhardness

Enamel Preparation for Testing Whitening Effects on Surface & Subsurface Microhardness & Fracture Susceptibility

1. Ameri, H., Ghavamnasiri, M., & Abed, A. (2011). Effects of different bleaching time intervals on fracture toughness of enamel. *Journal of conservative dentistry : JCD*, 14(1), 73–75. <https://doi.org/10.4103/0972-0707.80739>
2. White DJ, Kozak KM, Zoladz JR, Duschner HJ, Götz H. Effects of tooth-whitening gels on enamel and dentin ultrastructure--a confocal laser scanning microscopy pilot study. *Compend Contin Educ Dent Suppl*. 2000;(29):S29-34; quiz S43. PMID: 11908407.
3. Götz H, Duschner H, White DJ, Klukowska MA. Effects of elevated H₂O₂ 'strip' bleaching on surface and subsurface enamel including subsurface histomorphology, micro-chemical composition and fluorescence changes. *J Dent*. 2007 Jun;35(6):457-66. doi: 10.1016/j.jdent.2007.01.004. Epub 2007 Mar 6. PMID: 17339072.

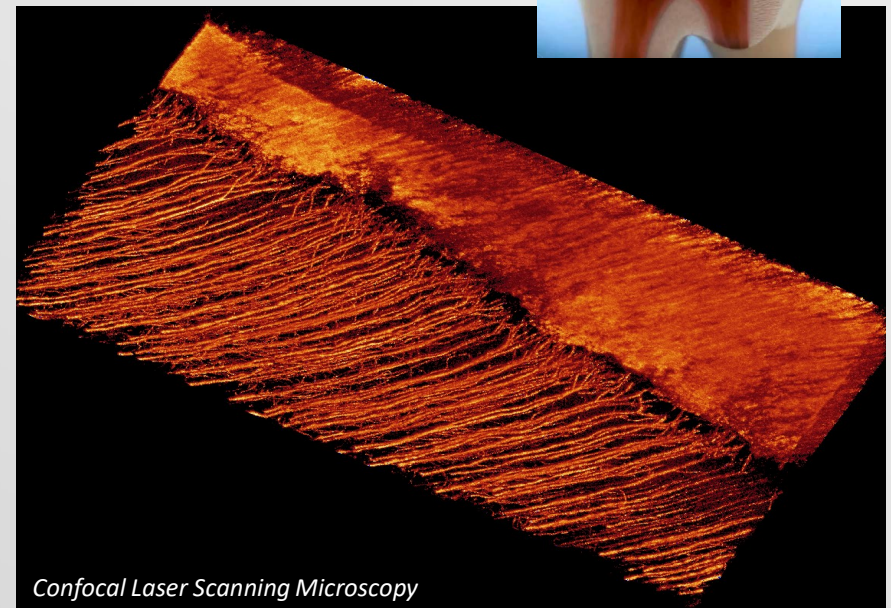


PEROXIDE SAFETY AND THE DENTIN

No Change in Surface Microhardness

No Change in Root Surface Morphology.

No evidence of smear layer solubilization



Confocal Laser Scanning Microscopy

Bleach Effects on DEJ Subsurface
Reconstruction in 2D and 3D non-destructive



PEROXIDE SAFETY AND RESTORATIVE MATERIAL

No substantial effects on bond strengths or leakage susceptibility of restoration preparations

Post-bleach bonding should take place 2 weeks after bleaching in agreement with literature observations

No Change in MICROLEAKAGE¹
from 70 hours Bleaching with 6.5 % HP

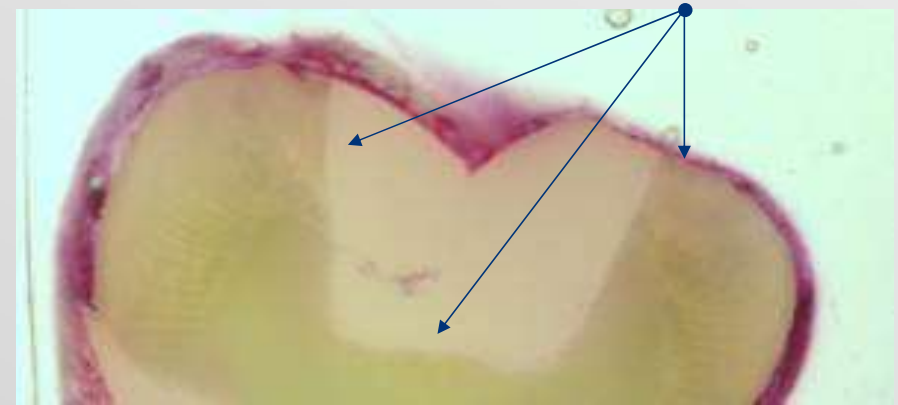
No Change in NANOLEAKAGE²
from 70 hours Bleaching with 6.5 %

No Significant Change in DENTIN BOND STRENGTH³
from 70 Hours Bleaching with 6.5 %



BOND STRENGTHS, MICROLEAKAGE, NANOLEAKAGE

Ensure treatment does not promote formation of gaps in margins or bond loosening





META-ANALYSIS ON THE SAFETY OF H₂O₂

Safety of vital tooth bleaching with 6% H₂O₂ Whitening

Strips: Evidence from 18 clinical trials

McMillan D, et al. J Dent Res (AADR/IADR) 2003;82. Abstract 1045

- 18 randomized clinical trials
- Treatment: 2x/day for 30 mins. each over 14 days
- 316 subjects

Conclusion

- Clinical safety and tolerability of Whitestrips with 6% H₂O₂ is established.
- Mild, transient tooth sensitivity (18%) and oral irritation (17%) were the most commonly reported adverse event.*

* Most resolved during treatment phase or within 1-2 days post-treatment.

<https://www.dentalcare.com/-/media/dentalcareus/research/pdf/cws/mcmillan2003.pdf?la=en&v=1-201604251148>