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REVIEW ARTICLE

*N Hossainian*
*DE Slot*
*F Afennich*
*GA Van der Weijden*

# The effects of hydrogen peroxide mouthwashes on the prevention of plaque and gingival inflammation: a systematic review

**Authors' affiliations:**
*N Hossainian*, *F Afennich*, School of Dental Hygiene, Hogeschool Utrecht, University of Applied Sciences, Utrecht, The Netherlands
*DE Slot*, *GA Van der Weijden*, Department of Periodontology, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands

**Corresponding to:**
*Dagmar Else Slot*
Department of Periodontology, Academic Centre for Dentistry Amsterdam (ACTA)
University of Amsterdam and VU University Amsterdam
Gustav Mahlerlaan 3004
1081 LA
Amsterdam
The Netherlands
Tel.: +31 20 5980 179/307
E-mail: d.slot@acta.nl

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**Abstract:** *Objectives:* The purpose of this review was to describe systematically the effects of hydrogen peroxide mouthwashes as an adjunct to daily oral hygiene or as a mono-therapy in the prevention of plaque accumulation and gingival inflammation. *Materials and methods:* PubMed-MEDLINE and the Cochrane-CENTRAL were searched up to December 2009 to identify appropriate papers. The primary outcome measures included plaque accumulation and parameters of gingivitis. *Results:* Independent screening of titles and abstracts of 229 articles resulted in 10 publications that met the criteria for eligibility. Descriptive comparisons are presented for hydrogen peroxide mouthwash as compared with control mouthwashes or no oral hygiene. Mean values and standard deviations were obtained by data extraction. Based on a quality assessment, three studies, of which one evaluated $H_2O_2$ over a period of 6 months, were considered to represent a low risk of bias. This 6-month study showed a positive effect of the use of $H_2O_2$ on the modified gingival index. *Conclusions:* The results of the studies included in this review showed that $H_2O_2$ mouthwashes do not consistently prevent plaque accumulation when used as a short-term mono-therapy. When used as a long-term adjunct to daily oral hygiene, the results of one study indicate that oxygenating mouthwashes reduce gingival redness.

**Key words:** bleeding; gingivitis; hydrogen peroxide mouthwash; hydrogen peroxide; plaque; systematic review

## Introduction

A classical study by Löe *et al.* (1), 'experimental gingivitis in man' demonstrated that the accumulation of bacterial plaque plays an essential role in the initiation and progression of periodontal disease. Regular mechanical removal of bacterial plaque appears to be a prerequisite for the prevention of periodontal disease (2). Several clinical studies have concluded that instruction in plaque control is mandatory as part of the therapy of periodontal diseases (2, 3). However, it has also been reported that the quality of self-performed mechanical plaque removal may not be sufficient (4). When mechanical plaque control fails or cannot be maintained, a chemical approach, such as the use of an antimicrobial mouthwash, can be an alternative or an adjunct (5).

The first reference to mouth rinsing as a formal practice is credited to Chinese medicine, about 2700BCE for treatment of disease of the gums (6). Since the 1960s, many antimicrobial agents have been studied as

mouth rinsing agents (7–9). Oxygenating agents, such as hydrogen peroxide ($H_2O_2$), buffered sodium peroxyborate and peroxycarbonate, have been recommended for short-term use to reduce the symptoms of pericoronitis (10). The use of $H_2O_2$ to decrease plaque formation and control periodontal disease was first reported in 1913 (11). Hydrogen peroxide exerts antimicrobial effects through the release of oxygen and antibacterial effects are seen in Gram-positive as well as Gram-negative organisms (12). Oxygenating agents have shown clear efficacy in the treatment of necrotizing gingivitis (13), and their use has been recommended in a narrative review by Mandel *et al.* (10). An earlier published narrative review by Eley (14) claims that although, $H_2O_2$ mouthwashes exhibit antibacterial effects *in vitro*, they have varying plaque inhibitory effects (from moderate to low or no statistical difference as compared with negative control) in clinical studies.

Several narrative reviews have been published concerning $H_2O_2$ mouthwashes. Most of these reviews have focused on $H_2O_2$ as a bleaching agent (15, 16).

This review is part of a series of systematic reviews on the effect of various chemotherapeutic agents (17–20). The present review was conducted to evaluate systematically the antiplaque and antigingivitis effectiveness of oxygenating mouthwashes in human clinical trials in humans.

## Materials and methods

### Focused question

What are the effects of oxygenating mouthwashes on plaque accumulation and parameters of gingival inflammation in adults, when compared with positive or negative control mouthwashes or to no oral hygiene, when used as a mono-therapy or as an adjunct to daily oral hygiene?

### Search strategy

Two internet sources were used to search for appropriate papers that satisfied the study purpose. These included the National Library of Medicine, Washington, DC. (PubMed-MEDLINE) and the Cochrane Central Register of Controlled Trials (CENTRAL). Both databases were searched for studies conducted in the period up to and including December 2009. The search was designed to include any published paper that evaluated the effects of $H_2O_2$-containing mouthwashes. All reference lists of the selected studies were screened for additional published work that could possibly meet the eligibility criteria of this study. For details, see Box 1.

Box 1. **Pubmed-MEDLINE and Cochrane-CENTRAL search**
The following terms were used in the search strategy:
[<Agent OR brandname> AND vehicle]
[<Agent: Hydrogen peroxide OR $H_2O_2$ OR Sodium peroborate OR Peroxyborate OR Peroxycarbonate
OR
Brandname: Bocasan OR Amosan OR Peroxyl OR Ascoxal>
AND
Vehicle: Mouthwashes OR Mouthwash OR Mouthwash* OR Mouthrinses OR Mouthrinse]

### *Eligibility criteria*

- Randomized clinical trials OR clinical controlled trials.
- Conducted in human adults ≥17 years in good general health.
- Intervention: $H_2O_2$-containing (oxygenating) mouthwashes used as a mono-therapy or as an adjunct to daily oral hygiene.
- Control mouthwashes (positive control: CHX; negative control: placebo, water, saline or no oral hygiene).
- Parameters to be mentioned in short-term studies (<4 weeks): plaque.
- Parameters to be mentioned in long-term studies (≥4 weeks): plaque, bleeding and gingivitis.

### Screening and selection

Papers were independently screened by two reviewers (NH and GAW), first for titles and then for abstracts. If information relevant to the eligibility criteria was not available in the abstract or if the title was relevant and the abstract was not available, the paper was selected for full text reading (DES and NH). As a next step, full-text papers that fulfilled the eligibility criteria were identified for inclusion into this study. Any disagreement between the two reviewers was resolved after additional discussion. If disagreement persisted, the judgement of a third reviewer (GAW) was decisive. Two reviewers (DES and NH) hand-searched the reference lists of all included studies for additional articles. Only papers written in English were accepted. Case reports, letters and narrative/historical reviews were not selected.

### Assessment of heterogeneity

The factors used to evaluate the heterogeneity of outcomes of different studies included
- Subjects and parameters of interest.
- Intervention and comparison.
- Regimen.
- Side effects and industry funding.

### Quality assessment

Two reviewers (DES and NH) scored the methodological quality of the included studies. Assessment of methodological quality was performed as proposed by the RCT checklist of the Dutch Cochrane Centre (21) and completed with quality criteria as obtained from the CONSORT statement (22), Esposito *et al.* (23), Moher *et al.* (24–27), Needleman *et al.* (28) and the Delphi List (29).

Criteria were designed to address each domain of external validity, internal validity and statistical methodology. An aspect of the score list was given a '+' for an informative

description of the item at issue for a study design that met the quality standard, a '–' for an informative description and a study design that did not meet the quality standard, and a '?' for missing or insufficient information. When random allocation, defined inclusion/exclusion criteria, blinding of both the patient and examiner, balanced experimental groups, identical treatment between groups except for intervention, and report of follow-up criteria were present, the study was classified as having a low risk of bias. Studies missing one of these five criteria were considered to have a moderate potential risk of bias. Studies missing two or more of these criteria were considered to have a high potential risk of bias. In addition, the Centre for Evidence-based Medicine (CEBM) 'Levels of Evidence' were used (30). In this system, the level of evidence is scored as follows. Score 1b- to individual RCTs with a narrow confidence Interval and 1b- to individual RCTs with a wide confidence Interval. Score 2b is given to individual cohort studies, including low-quality RCTs, e.g. more than 20% of dropout.

#### Data extraction

From the selection of papers that met the criteria, data were extracted with regard to the effectiveness of mouthrinsing with $H_2O_2$ mouthwash in comparison with a control treatment (CHX, placebo, saline or no treatment/no oral hygiene). Mean values and SD of plaque and gingivitis parameters were extracted (NH and DES). Some of the papers provided standard errors (SE) of the mean. Where possible, the authors calculated the SD based on the sample size ($SE = SD/\sqrt{N}$). When intermediate measures were presented, the longest evaluation term reported was used for this review.

#### Data analysis

After a preliminary evaluation of the selected papers, it was found that considerable heterogeneity was present in the study designs, characteristics, outcome variables and results. It was therefore not possible to perform a valid quantitative analysis of the data and subsequent meta-analysis. Instead, a descriptive manner of data presentation was used.

## Results

#### Search and selection results

In the PubMed-MEDLINE and Cochrane-CENTRAL searches, a total of 229 unique, potentially suitable papers were found. Initial screening of the title and abstracts resulted in 18 articles for full-text reading, of which eight papers were excluded because they failed to fulfil the inclusion criteria of this review, and one was not included due to irretrievability (39). An overview of these studies, including the reasons for exclusion after full-text reading, is given in Table 1. Additional hand-searching of reference lists of the selected studies resulted in the inclusion of one additional paper from the reference list of Wennström & Lindhe (48), namely Bergenholtz *et al.* (40).

Table 1. **Overview of the studies that were excluded after full text reading**

| Reference | Reason for rejection |
|---|---|
| Shibly *et al.* (31) | $H_2O_2$ used as toothpaste |
| Binney *et al.* (32) | No evaluation of the active ingredient |
| Maruniak *et al.* (33) | $H_2O_2$ used in combination with other active ingredients |
| Boyd (34) | Subjects had fixed orthodontic appliance |
| Clark *et al.* (35) | Rinsing was combined with subgingival irrigation |
| Martini (36) | Insufficient data presentation |
| Addy and Llewelyn (37) | Inappropriate evaluation for this review |
| Johansen *et al.* (38) | $H_2O_2$ not used in a mouthwash form |
| Behrman (39) | Irretrievable |

Finally, ten papers with twelve experiments were processed for data extraction, where Bergenholtz *et al.* (40) and Jones *et al.* (46) each presented two useful experiments (Fig. 1).

#### Assessment of study heterogeneity

Considerable heterogeneity was observed in the interventions, regimens, concentrations, evaluation period and outcome variables used in the studies reported in the 10 selected papers. The number, gender and age of participants also varied among the studies. Table 2 presents information regarding the study characteristics.

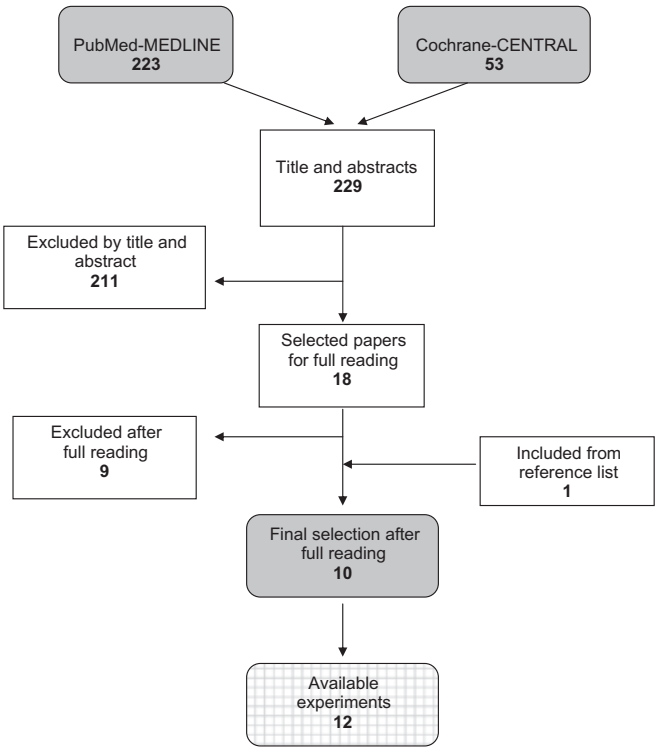


*Fig. 1.* Search and selection results.

Table 2. **Overview of the selected studies processed for data extraction**

| Weeks | # | Reference | Design and evaluation period | # subjects, gender and age, periodontal status | Comparison | Conclusion |
|---|---|---|---|---|---|---|
| <4 | Ia | Bergenholtz *et al.* (40) | RCT<br>Single blind<br>Cross-over<br>3 days | Subjects: 16<br>♀: 8<br>♂: 8<br>Mean age: ?<br>Age range: 18–24 years<br>Clinically healthy periodontal tissues | Sodium percarbonate (?%)<br>Sodium perborate (?%)<br>Placebo<br>No oral hygiene | Sodium percarbonate and sodium perborate mouthwash did not inhibit the formation of plaque when used for 2 min four times a day for 3 days |
| | Ib | | | Subjects: 16<br>♀: 8<br>♂: 8<br>Mean age: ?<br>Age range: 18–24 years<br>Clinically healthy periodontal tissues | Sodium percarborate (?%)<br>Distilled water<br>No oral hygiene | It is evident that when used for 3 days, the sodium percarborate mouthwash inhibits plaque formation. At the same time, however, use of the mouthwash was followed by observable changes in the mucosa, and this means that this preparation is quite unsuitable for clinical use |
| | II | Binney *et al.* (41) | RCT<br>Cross-over<br>Single blind<br>4 days | Subjects: 18<br>♀:8<br>♂: 10<br>Mean age: ?<br>Age range: 20–29 years<br>High standard of oral hygiene and gingival health | Sodium perborate (?%)<br>CHX (0.2%)<br>Saline | From a zero baseline, plaque regrowth at day 5 was significantly reduced by CHX compared with peroxyborate and, in turn, was significantly reduced by peroxyborate compared with saline |
| | III | Chadha *et al.* (42) | CCT<br>Blinding: ?<br>Cross-over<br>8 days | Subjects: 15<br>♀: ?<br>♂: 15<br>Mean age: ?<br>Age range: 18–22 years<br>Healthy periodontium | Sodium peroxyborate monohydrate bitartarate (?%)<br>No oral hygiene | With sodium peroxyborate monohydrate bitartarate rinsing 30.62% less plaque accumulation was found when that regimen was compared with no oral hygiene |
| | IV | Gomes *et al.* (43) | RCT<br>Parallel<br>Double blind<br>7 days | Subjects: 74<br>♀: 64<br>♂: 10<br>Mean age: ?<br>Age range: 20–51 years<br>Free of advanced periodontal disease (pocket depth not greater than 5 mm) | $H_2O_2$ (1.5%)<br>Placebo | The supervised use of a 1.5% hydrogen peroxide mounthrinse (Peroxyl) reduced plaque in individuals with mild-to-moderate initial levels of gingivitis and plaque accumulation |

Table 2. (*Continued*)

| Weeks | # | Reference | Design and evaluation period | # subjects, gender and age, periodontal status | Comparison | Conclusion |
|---|---|---|---|---|---|---|
| | V | Gusberti *et al.* (44) | CCT<br>Parallel<br>Blinding?<br>21 days | Subjects: 32<br>♀:?<br>♂: ?<br>Mean age: ?<br>Age range: ?<br>Plaque and gingival indices approaching zero | $H_2O_2$ (1%)<br>CHX (0.12%)<br>Placebo | The group using 1% $H_2O_2$ showed no significant reduction in plaque scores |
| | VI | Hoenderdos *et al.* (45) | RCT<br>Double blind<br>Parallel<br>3 days | Subjects: 39<br>♀: ?<br>♂: ?<br>Mean age: 24.5<br>Age range: 19–42 years<br>Healthy periodontium | $H_2O_2$ (0.013%)<br>Placebo | The results of this pilot study showed that there was no statistically significant difference between the $H_2O_2$ group and the placebo group with respect to plaque inhibition within this study design |
| | VIIa and VIIb | Jones *et al.* (46) | RCT<br>Parallel<br>Double blind<br>a; 7 days treatment phase<br>b; 7 days preventive phase | Subjects: 45<br>♀: 19<br>♂: 26<br>Mean age: ?<br>Age range: 17–39 years | $H_2O_2$ (1.5%)<br>Placebo | At no time, there was any statistical difference between either of the experimental groups and/or the placebo group in terms of plaque scores |
| | VIII | Moran *et al.* (47) | RCT<br>Single blind<br>Cross-over<br>4 days | Subjects: 16<br>♀/♂: ?<br>Mean age: ?<br>Age range: ?<br>High standard of oral hygiene and gingival health | Sodium peroxyborate (?%)<br>CHX (0.2%)<br>Sodium peroxycarbonate (?%)<br>Saline | The findings of these studies would suggest oxidizing mouthrinses may inhibit plaque formation |
| | IX | Wennström and Lindhe (48) | CCT<br>Double blind<br>Cross-over<br>14 days | Subjects: 14<br>♀: ?<br>♂: ?<br>Mean age: ?<br>Age range: ?<br>No sign of active periodontal breakdown | Sodium perborate (?%)<br>Placebo | The mouthwash, which was used as the only oral hygiene measure during a 2-week period, markedly reduced the amount of plaque formed |
| ≥4 | X | Hasturk *et al.* (49) | RCT<br>Double blind<br>Parallel<br>6 months | Subjects:<br>Baseline; 99<br>End; 78<br>♀: 41<br>♂: 37<br>Mean age: 31<br>Age range: 18–50 years<br>Gingivitis | Fluoridated $H_2O_2$ (1.5%) + OH<br>Placebo + OH | The results of this study indicate that the fluoridated hydrogen peroxide-based mouthrinse significantly reduces gingivitis |

OH, daily oral hygiene; ?, not specified/unclear.

#### *Subjects and parameters of interest*

In four studies, the selected subjects were dental students or dental assistants, technicians, nurses and hygienists (# I, III, V, IX). Study (# IX) presented the plaque score as the frequency of index scores from 0 to 3 and did not provide overall mean plaque scores.

#### *Intervention and comparison*

Table 2 presents an overview of the comparisons. The $H_2O_2$ mouthwashes used in these studies included several brands: Amosan® Oral-B (# IX), Ascoxal (# Ia), BioXyl® (# VI), Bocasan Oral-B, Aylesbury, England (# II, VIII), Bocosept (# Ia), Kavosan Oral-B, Frankfurt (# VIII), Germany, Peroxyl® (# IV) and Rembrandt, Den-Mat Corporation, Santa Maria, California (# X). No brand description was provided in four studies (# Ib, III, V, VII). Consequently, the mouthwashes used in the studies contained different concentrations.

The following placebo solutions were used: an identically flavoured rinse without $H_2O_2$ (# VII), a rinse with an identical base formulation (# IV, X), a flavoured alcoholic solution (# V), and a red-tinted flavouring agent (# I). The placebo mouthrinse of # VI did not contain $H_2O_2$ but only contained 0.004% glycerol dissolved in demineralized water. In one study, rinsing was performed as an adjunct to daily oral hygiene (# X), while in the other studies, oral hygiene was suspended during the rinsing period and $H_2O_2$ was used as mono-therapy (# I, II, III, IV, V, VI, VII, VIII, IX).

#### *Regimen*

Oral treatment regimes substantially varied in terms of rinsing time and the amount of mouthwash used, as well as in whether they included instruction in and/or supervision of oral hygiene. A baseline prophylaxis was given in all but two studies (# IV, V). Supervised rinsing was performed in two studies (# IV, V) where in one of these studies (# V), subjects performed rinsing under supervision on weekdays and without supervision on weekends. Oral hygiene instructions were provided in two studies (# VII, X). The remaining studies (# I, II, III, IV, V, VI, VII, IX) provided no details concerning oral hygiene instructions. In seven studies, rinsing was performed twice daily with $H_2O_2$ or with control rinses (# II, III, V, VI, VII, VIII, X). In two studies, subjects rinsed three times a day (# IV, IX), and while in one study (# I), they rinsed four times a day. Rinsing volumes varied between studies; 10 ml (# II, IV); 15 ml (# III, V, VII); 15–20 ml (#VI); 25 ml (# I) and 30 ml (# VIII, IX). In one study, no information was given concerning the amount of mouthwash used (# X). Rinsing times varied from 20 (#VI), 30 (# III, V, X) or 60 s (# II, IV, VIII) to 2 min (# I, VII, IX).

#### *Side effects and industry funding*

Three studies reported on side effects (# I, V, X); two of these observed no side effects, such as tooth staining, mucosal irritation or taste alternation (# V, X). In one study (# Ib), two subjects experienced a painful sensation in the mouth when using $H_2O_2$ mouthwash, whereas in two cases, erosive changes of the oral mucosa were seen. No adverse events were reported by the subjects and the examiners of study # VI. Funding was mentioned in seven studies including Den-Mat Corporation, Santa Maria, California (# X); Oral B Company, USA (# VIII); Colgate-Palmolive Limited (# VII); The Procter & Gamble Company, Cincinnati, Ohio and Miami Valley Laboratories, USA (# V); Hoyt Laboratories, Norwood, Massachusetts (# IV) and Patentmedelsfonden för odontologics profylaxforskning (# I). In study # VI, ClearWater Revival B.V. (Amsterdam, Holland) provided the test products.

### Quality assessment

Quality assessment values, including external, internal and statistical validity, are presented in Table 3. Based on a summary of these criteria, the estimated potential risk of bias is low in four of the ten studies (# IV, VI, VII, X). The potential risk is considered moderate for two studies (# II, VII) and high for four studies (# I, III, V, IX). Two studies received a score of 1B (# VIII, X) and four studies 1B, as they lacked confidence intervals (# II, IV, VI, VII). Four studies exhibited low quality RCTs with a 2B score (# I, III, V, IX).

### Study outcome results

#### *Comparison of baseline and end scores (within groups)*

Differences between the baseline and end scores are shown in Table 4 (a–c).

*Short-term effect on the plaque index (Table 4a):* Eight out of nine studies that provided data on the plaque index did not present statistical analysis with respect to changes in time for each group. One short-term study reported a significant reduction in plaque scores for the group using a $H_2O_2$ mouthwash (# IV).

*Long-term effects on the plaque index and gingival index (Table 4b–c):* A single long-term study showed a significant reduction in the modified gingival index (MGI) (54) and the eastman interdental bleeding index (EIBI) (55) in subjects using the $H_2O_2$ mouthwash (# X, low risk of bias). In this particular study, rinsing was performed as an adjunct to daily oral hygiene.

#### *Comparisons between groups*

Differences between $H_2O_2$ mouthwashes and control treatments are presented in a descriptive manner in Table 5 (a–b).

*Short-term effect on the plaque index (Table 5a):* Compared with no oral hygiene, $H_2O_2$ resulted in a positive effect on plaque in one of three studies (# Ib). When compared with distilled water, saline or a placebo, $H_2O_2$ was significantly more effective in three studies (# Ib, II, VIII). In comparison with CHX, $H_2O_2$ was significantly less effective (# II, V, VIII).

Table 3. **Methodological quality scores of the selected studies**

| Weeks | | <4 | | | | | | | | | ≥4 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Quality criteria | Study | I | II | III | IV | V | VI | VII | VIII | IX | X |
| Internal validity | Random allocation | + | + | − | + | − | + | + | + | − | + |
| | Allocation concealment | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? |
| | Blinded to patient | − | − | ? | + | ? | + | + | − | + | + |
| | Blinded to examiner | + | + | ? | + | ? | + | + | + | + | + |
| | Blinding during statistical analysis | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? |
| | Balanced experimental groups | + | + | + | + | + | + | + | + | + | + |
| | Reported loss to follow up | − | + | + | + | − | + | + | + | − | + |
| | # of dropouts | ? | 0◇ | 0◇ | 0◇ | ? | 1◇ | 2.2◇ | 0◇ | ? | 21◇ |
| | Treatment identical, except for intervention | + | + | + | + | + | + | + | + | + | + |
| External validity | Representative population group | + | + | + | + | + | + | + | + | + | + |
| | Eligibility criteria defined | − | + | + | + | + | + | + | + | + | + |
| Statistical validity | Sample size calculation and power | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? |
| | Point estimates | + | + | + | + | + | + | + | − | − | − |
| | Measures of variability presented for the primary outcome | + | + | − | − | + | + | + | + | − | − |
| | Include an intention-to-treat analysis | ? | + | + | + | ? | ? | ? | + | ? | + |
| | Authors estimated risk of bias | High | Moderate | High | Low | High | Low | Low | Moderate | High | Low |
| | Levels of evidence (30) | 2b | 1b− | 2b | 1b− | 2b | 1b− | 1b− | 1b | 2b | 1b |

For abbreviations, see Table 2.
+, yes; −, No; ?, unclear; ◇, calculated by the authors.

*Long-term effects on the plaque and gingival indices (Table 5b):* When used as an adjunct to daily oral hygiene, one long-term study in this review (# X) showed a significant effect of $H_2O_2$ on the MGI compared with placebo. No such effect was seen for bleeding scores.

## Discussion

A systematic review can be defined as the process of systematically locating, appraising and synthesizing evidence from scientific studies to obtain a reliable overview (56). This systematic review was performed to identify the efficacy of oxygenating mouthwashes on plaque accumulation and parameters of gingivitis. The outcome of this review concerning a plaque inhibiting effect is inconclusive and just one study of ≥4 weeks was available, which showed a small but significant effect on gingivitis. Some important considerations concerning the outcome of this review are discussed below.

### Evaluation period

According to Gunsolley (57), short-term studies (4 days to 2 weeks) can be used to investigate antiplaque effects. Intermediate-length trials (2 weeks to 2 months), which allow for the assessment of gingivitis, have limitations in that they may not reflect the patients' actual long-term use of the product (57). The ADA requirements for a seal of acceptance require a study period of 6 months to evaluate both the efficacy and safety of chemical agents as well as patients' compliance (58). Given that mouthrinses are also used and prescribed for short periods, their efficacy over shorter periods remains of interest (59). Consequently, studies with an evaluation period of less than 4 weeks were also included in this review. Concerning adjunctive devices for controlling plaque and gingivitis, the ADA demands an evaluation period of at least 4 weeks (60). Therefore, selected studies of 4 weeks or more in duration were considered for extraction of both plaque and gingivitis data. In concordance with ADA requirements, gingival inflammation data were not evaluated for short-term studies (<4 weeks).

### Regimen

Several factors are necessary for the antimicrobial effect of $H_2O_2$ to occur. Concentration and length of exposure are the most important factors (15). The regimens used in the reviewed clinical trials varied substantially in rinsing time and amount of mouthwash used. Also, the duration of the experimental periods most often varied from 3 (# I, VI) to 21 days (# V), with one study lasting 6 months (# X). When evaluating the short-term effect of $H_2O_2$ as a mono-therapy without taking rinsing time and the amount of mouthwash into account, three of the ten studies found differences in the plaque-inhibiting effects of $H_2O_2$ compared with negative control. The single long-term study (# XI) showed positive results of $H_2O_2$ on the reduction of gingival inflammation when used as an adjunct to daily oral hygiene. This study (# XI) evaluated the efficacy of the active mouthwash versus placebo mouthwash in reducing gingivitis, based on changes in gingival inflammation as assessed by MGI (54) during the trial. Changes in bleeding index parallel to MGI scores were found not to be statistically significant between the groups. Furthermore, this study did not observe an effect on plaque as compared with a placebo, despite the long-term use of $H_2O_2$.

Table 4. **Overview of selected studies and ordered by assessment parameters. (a) Short-term effect on plaque index, (b) long-term effects on the plaque index, (c) long-term effects on the gingival health**

| # | Index | Groups | Baseline | End | Difference | Significant difference within groups |
|---|---|---|---|---|---|---|
| (a) | | | | | | |
| VIIa | Silness and Löe (50) | $H_2O_2$ (1.5%) | 1.04 (0.13) | 1.15 (0.13) | +0.11◇ | ? |
| | | Placebo | 1.09 (0.18) | 1.19 (0.18) | +0.10◇ | ? |
| VIIb | | $H_2O_2$ (1.5%) | 0.26 (0.15) | 1.10 (0.15) | +0.84◇ | ? |
| | | Placebo | 0.32 (0.20) | 1.14 (0.15) | +0.82◇ | ? |
| V | Silness and Löe (50) | $H_2O_2$ (1%) | 0.01 | 1.41 | +1.40◇ | ? |
| | | CHX (0.12%) | 0.01 | 0.36 | +0.35◇ | ? |
| | | Placebo | 0.01 | 1.57 | +1.56◇ | ? |
| IV | Silness and Löe (50) | $H_2O_2$ (1.5%) | 0.62◇ | 0.46◇ | −0.16◇ | Yes |
| | | Placebo | 0.46◇ | 0.45◇ | −0.01◇ | No |
| IX | Silness and Löe (50) | Sodium perborate (?%) | 0.01◇ | 0.63◇ | +0.62◇ | ? |
| | | Placebo | 0.01◇ | 1.30◇ | +1.29◇ | ? |
| Ia | Silness and Löe (50) | Sodium percarborate (?%) | 0.9 (0.4) | 1.2 (0.5) | +0.3◇ | ? |
| | | Sodium perborate (?%) | 0.7 (0.3) | 1.2 (0.5) | +0.5◇ | ? |
| | | Placebo | 0.8 (0.3) | 1.6 (0.5) | +0.4◇ | ? |
| | | No oral hygiene | 0.7 (0.4) | 1.3 (0.5) | +0.6◇ | ? |
| Ib | Silness and Löe (50) | Sodium percarbonate (?%) | 0.6 (0.2) | 0.7 (0.4) | +0.1◇ | ? |
| | | Distilled water | 0.7 (0.1) | 1.1 (0.4) | +0.4◇ | ? |
| | | No oral hygiene | 0.8 (0.2) | 1.3 (0.3) | +0.5◇ | ? |
| VIII | Quigley and Hein (51) | Sodium peroxyborate (?%) | 0 | ? | ? | ? |
| | Modified by Turesky (52) | CHX (0.2%) | 0 | ? | ? | ? |
| | | Sodium peroxycarbonate (?%) | 0 | ? | ? | ? |
| | | Saline | 0 | ? | ? | ? |
| II | Quigley and Hein (51) | Sodium perborate (?%) | ? | 1.94 (0.31) | ? | ? |
| | Modified by Turesky (52) | CHX (0.2%) | ? | 1.60 (0.31) | ? | ? |
| | | Saline | ? | 2.28 (0.33) | ? | ? |
| VI | Quigley and Hein (51) | $H_2O_2$ (0.013%) | 0 | 2.66 (0.29) | +2.66 ◇ | ? |
| | Modified by Turesky (52) and Lobene *et al.* (53) | Placebo | 0 | 2.70 (0.32) | +2.70 ◇ | ? |
| III | Quigley and Hein (51) | Sodium peroxyborate monohydrate bitartarate (?%) | 0 | 4.44◇ (0.51◇) | +4.44◇ | ? |
| | | No oral hygiene | 0 | 6.41◇ (0.61◇) | +6.41◇ | ? |
| (b) | | | | | | |
| X | Quigley and Hein (51) | Fluoridated $H_2O_2$ (1.5%) + OH | 1.03 | 0.989◇ | −0.041 | No |
| | Modified by Turesky (52) | Placebo rinse + OH | 0.87 | 0.991◇ | +0.121 | No |
| (c) | | | | | | |
| X | Modified Gingival Index | Fluoridated $H_2O_2$ (1.5%) + OH | 1.81 | 1.628◇ | −0.182 | Yes |
| | Gordon *et al.* (54) | Placebo + OH | 1.79 | 1.831◇ | +0.041 | No |
| X | Eastman interdental bleeding index | Fluoridated $H_2O_2$ (1.5%) + OH | 0.053 | 0.0189◇ | −0.0341 | Yes |
| | Polson *et al.* (55) | Placebo + OH | 0.038 | 0.0146◇ | −0.0234 | Yes |
| X | Bleeding index | Fluoridated $H_2O_2$ (1.5%) + OH | 0.119 | 0.101◇ | −0.018 | No |
| | | Placebo + OH | 0.100 | 0.082◇ | −0.018 | No |

For abbreviations, see Table 3.

#### $H_2O_2$ formulations

The selected studies used mouthrinses containing 0.013%–1.5% $H_2O_2$. However, no information is provided concerning the optimal therapeutic level of $H_2O_2$. Gusberti *et al.* (44) concluded that mouthrinses containing 1% $H_2O_2$ did not provide meaningful anti-plaque or antigingivitis benefits. The review of Marshall *et al.* (15) also stated that efficacy of $H_2O_2$ was not associated with use of $H_2O_2$ at <1%. The concentration $H_2O_2$ that was used for study # VI (45) was much lower as the above-mentioned concentrations. The manufacturer considered the addition of glycerol sufficient to improve stability and ensured an antiplaque effect. However, the plaque growth inhibiting effect of 0.013% $H_2O_2$ combined with 0.004% glycerol was found to be insignificant within the present study design (45).

#### Combinations of $H_2O_2$

Hydrogen peroxide mouthwashes are also used in combination with other mouthwashes. Research has been carried out over the past several years on the effect of $H_2O_2$ with respect to the inhibition of stain formation following the use of CHX. Positive results with respect to plaque inhibition have been

Table 5. **(a) Summary of study outcomes (<4 weeks) whether there is a significant effect in favour of the $H_2O_2$ mouthwash with respect to plaque scores compared with the control groups ordered according to the comparison. (b) Summary of the study (≥4 weeks) whether there is a significant difference in favour of the $H_2O_2$ mouthwash with respect to plaque scores and gingival indices compared with the control group**

| # | Intervention | Plaque | Comparison |
|---|---|---|---|
| (a) | | | |
| III | Sodium peroxyborate monohydrate bitartarate (?%) | ? | No oral hygiene |
| Ia | Sodium perborate (?%) | NS | |
| Ia | Sodium percarbonate (?%) | NS | |
| Ib | Sodium percarbonate (?%) | + | |
| VI | $H_2O_2$ (0.013%) | NS | Negative control rinse |
| V | $H_2O_2$ (1%) | NS | |
| IV | $H_2O_2$ (1.5%) | ? | |
| VIIa | $H_2O_2$ (1.5%) | NS | |
| VIIb | $H_2O_2$ (1.5%) | NS | |
| Ia | Sodium perborate (?%) | NS | |
| II | Sodium perborate (?%) | + | |
| IX | Sodium perborate (?%) | ? | |
| Ia | Sodium percarbonate (?%) | NS | |
| Ib | Sodium percarbonate (?%) | + | |
| VIII | Sodium peroxyborate (?%) | + | |
| VIII | Sodium peroxycarborate (?%) | + | |
| II | Sodium perborate (?%) | – | CHX (0.2%) |
| VIII | Sodium perborate (?%) | – | |
| VIII | Sodium peroxycarborate (?%) | – | |
| V | $H_2O_2$ (1%) | – | CHX (0.12%) |

| # | Intervention | Plaque | Gingival index | Bleeding | Comparison |
|---|---|---|---|---|---|
| (b) | | | | | |
| X | Fluoridated $H_2O_2$ (1.5%) + OH | NS | + | NS | Placebo |

For abbreviations, see Table 4. +, effect significantly larger than comparison; –, effect significantly smaller than comparison; NS, no significant difference; ?, effect not described.

reported when CHX is combined with oxidizing agents, such as $H_2O_2$, peroxy-monosulfate, or Bocasan® (61–65). In a study by Dona *et al.* (66), the combination of chlorhexidine (CHX) and Bocasan® was tested and resulted in statistically significant lower plaque scores as compared with CHX alone in a 3-day plaque accumulation model. In a study conducted by Grundemann *et al.* (64), the combination of these two mouthwashes was compared with CHX alone in a 14-day non-brushing protocol. The combination resulted in significant improvements for stain, plaque and bleeding. These findings agree well with other studies that investigated the synergistic effects of mouthwashes. Charbonneau *et al.* (67) tested a combination of CHX and monoperoxyphtalic acid in beagle dogs. Steinberg *et al.* (68) assessed the synergistic effects of CHX and $H_2O_2$ in an *in vitro* study. Both studies indicated a superior effect of the combination of CHX and an oxygenating agent compared with CHX alone.

A recent study by Rosema *et al.* (69), evaluated a preventive programme which consisted of one oral hygiene instruction, one oral prophylaxis followed by rinsing for 3 weeks with a combination of chlorhexidine and sodium peroxyborate. It showed a beneficial effect on oral/gingival health that lasted up to 9 months. Future research could focus on the preventive impact of the mouthrinse combination by itself.

### Safety of $H_2O_2$

It has been suggested that the concentration of $H_2O_2$ is associated with varying side effects (15, 16, 70). Only two studies in this review did not report on $H_2O_2$ concentration. All of the included studies in which $H_2O_2$ concentration was reported used an $H_2O_2$ concentration of ≤1.5%. Only one study (# Ib), in which the concentration of $H_2O_2$ used was unknown, reported side effects, such as a painful sensation in the mouth and/or erosive changes of the oral mucosa. Variable responses of soft tissues when exposed to weaker $H_2O_2$ solutions have been reported in the literature. There are isolated reports of patients who developed oral ulcerations after using 3% $H_2O_2$ for 1–2 min 3–5 times daily (70), while at a lower concentrations, changes are less marked, even with continuous exposure. These results agree with those of the majority of the studies included in this review. Based on the selected studies, it can be concluded that the use of products containing low concentrations of $H_2O_2$ (≤1.5%) on a daily basis over an extended period of time does not induce serious side effects.

### Limitations of this review

A systematic review is limited by what is available in the existing dental literature. The search resulted in just one study that had an evaluation period of more than 4 weeks. Therefore, the outcome of this review with respect to levels of gingival inflammations is based on a single experiment with an estimated low risk of bias. In the studies of less than 4-week duration, only the outcome of plaque accumulation was extracted. Most of these studies ($N = 6$) had an evaluation period of just 1 week or less. Clearly, this is not sufficient to draw any conclusions on the long-term effects of $H_2O_2$ on plaque levels.

## Conclusion

The results of the studies included in this review show that $H_2O_2$ mouthwashes do not consistently effect plaque accumulation when used as a short-term mono-therapy. When used as long-term adjuncts to daily oral hygiene, the results of one study indicate that $H_2O_2$ mouthwashes reduce the early signs of gingival inflammation.

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