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Professionally-applied chemically-induced whitening of teeth in adults (Protocol)

Carrasco-Labra A, Brignardello-Petersen R, Yanine N, Araya I, Rada G, Chadwick RG

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Professionally-applied chemically-induced whitening of teeth in adults.
Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD010379.
DOI: 10.1002/14651858.CD010379.

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[Intervention Protocol]

Professionally-applied chemically-induced whitening of teeth in adults

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Editorial group: Cochrane Oral Health Group.
Publication status and date: New, published in Issue 2, 2013.

Citation: Carrasco-Labra A, Brignardello-Petersen R, Yanine N, Araya I, Rada G, Chadwick RG. Professionally-applied chemically-induced whitening of teeth in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD010379. DOI: 10.1002/14651858.CD010379.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

- To assess the effects of tooth whitening products developed to be professionally-applied with chemical, bleaching action (in-office).
- To evaluate the effects of complementary application of accelerators during bleaching therapy (heat, light or laser).

BACKGROUND

Description of the condition

The importance of teeth and smile in the context of facial attractiveness has been well established. The lower third of the face has a significant influence on the perception of beauty (Mack 1996), and teeth are considered the most important facial feature, followed by eyes (Jørnung 2007). The presence of noticeable discolouration of the teeth can be a physical handicap that can impact upon a person's self image, self confidence, physical attractiveness and employability. The demand for aesthetic dentistry has increased in recent years, particularly for tooth whitening. Surveys undertaken in the United Kingdom (Alkhatib 2004), the United States (Odioso 2000) and China (Xiao 2007) report that between 34% and 52% of adults are dissatisfied with the colour of their teeth. Discolouration may be due to either extrinsic staining on the surface of the tooth or caused by a change to the structural form or composition of the dental hard tissue producing intrinsic discolouration (Haywood 2006).

Extrinsic discolouration is present on the surface of the enamel or acquired pellicle and may arise from chromatogenic agents, the most common found in dietary products e.g. coffee, tea, red wine and tobacco (both traditional and smokeless). Poor oral hygiene can exacerbate and perpetuate extrinsic stains (Boksman 2006). Intrinsic discolouration may be due to a metabolic disease or systemic factors e.g. porphyria, antibiotic tetracycline staining, fluorosis, aging, caries, amalgam restorations, haemorrhage or pulp

necrosis (Fasanaro 1992; Haywood 2006).

Discolouration may be due to one or a combination of factors. It is important to identify the cause prior to treatment, therefore an exhaustive clinical examination and history should be undertaken in order to determine, as accurately as possible, the causal agent and to provide the patient with an accurate prognosis before any treatment is administered. Intrinsic stains are more difficult or impossible to eliminate using bleaching agents compared to discolouration caused by external chromatogenic substances (Boksman 2006). Bleaching may be achieved by agents applied professionally or for use at home. This review will focus on professional bleaching (applied in professional clinics only) and assisted bleaching (professional in-practice whitening as a supplement to home bleaching).

Description of the intervention

Most bleaching techniques involve peroxide or peroxide related products. Hydrogen peroxide was used for whitening teeth over 100 years ago, in 1884 by Harwan (Feinman 1987), however, its first use in dentistry was to treat periodontal disease (Wennström 1979). Professional bleaching was the first bleaching technique to be developed (Matis 2009). A higher strength of bleaching agent is used (e.g. 30% to 50% hydrogen peroxide) compared to home-based treatments (e.g. 10% to 22% carbamide oxide or 3% hydrogen peroxide). A current feature of professional bleaching is the use of an activator or accelerant agent to provide power bleaching. Application of heat, light, laser, or a combination, is used to increase the temperature of the bleaching agent in contact with the tooth surface (Weinberg 1997). A systematic review of activators concluded that superiority of accelerant over non-activated bleaching therapies is still debatable (Buchalla 2007). The aim of professional bleaching is to obtain the greatest improvement in as few sessions as possible (Goldstein 1997). Whilst this method of bleaching is faster than home-based techniques, it is more expensive but suitable for those who do not tolerate the use of trays (Boksman 2006). In the United States of America, around 50% of dentists provide professional bleaching, however, only 40% say they are "very satisfied" with the results of this technique (Weisman 2002).

Home bleaching is performed by the individual, and many systems require a custom-made tray worn for a few hours at a time, or overnight, to keep the bleaching agent against the teeth. Assisted bleaching can either be a series of treatments within a practice alone, or a supplement to boost home bleaching. The concentrations of bleach are higher than home bleaching (e.g. 30% to 44% carbamide peroxide) and it is popular because it does not require the gums to be protected. Power professional bleaching uses the highest concentration of bleaching agent and the gingiva require protection with either a rubber dam or resin shield.

In a review of the safety of bleaching procedures, no evidence was found for events such as pulpal necrosis or brittleness fracture (Fasanaro 1992). However, other types of adverse effects or harms, including those due to poor technique, have been reported, and these include soft tissue burns and tooth sensitivity (Haywood 2006; Jorgensen 2002). A direct association between tooth sensitivity and duration and dose of bleaching agent has been reported (Boksman 2006).

How the intervention might work

The bleaching action of hydrogen peroxide is not fully understood (Kihn 2007). However, the underlying chemical theory suggests two possible explanations.

1. Hydrogen peroxide breaks down into two components, forming a free-radical molecule (HO_2-) with high oxidative power, which would break-up macromolecular stains (Fasanaro 1992).
2. Peroxide opens the carbon-ring of pigments, transforming them into chains, which would give an appearance lighter in colour (Haywood 2001).

When a photochemical accelerator like light or laser is used, the rate of formation of hydroxyl radicals increases (Kashima-Tanaka 2003). Carbamide peroxide has a different chemical mechanism with other intermediary molecules, however, the final free-radical molecule is the same (Haywood 2001). Either hydrogen peroxide or carbamide peroxide final products diffuse into the tooth through the organic matrix of enamel and dentin, due to their low molecular weight, reaching the internal portion of the tooth within minutes (Bowles 1987; Cooper 1992). As soon as chromatogenic agents are transformed by the action of treatment into colourless molecules, the bleaching process reaches a plateau and no extra benefit can be obtained through further administration (Haywood 2006).

Why it is important to do this review

Professionally-applied bleaching treatments have been used for a long time, with a variety of products and different concentrations of active substances, resulting in a large body of research literature. In addition, methods for evaluating the effectiveness of one regimen of in-office bleaching compared to another are not standardised. Despite all of the information available, it is difficult for clinicians to determine which is the most effective treatment for tooth discolouration and the level of potential harms of these treatments. A systematic approach to summarise, organise and critically assess the evidence about the beneficial and adverse effects of in-office, professionally-applied chemically-induced whitening of teeth in adult patients is required to complement another Cochrane systematic review of the evidence for the use of home-based treatment methods (Hasson 2006).

OBJECTIVES

- To assess the effects of tooth whitening products developed to be professionally-applied with chemical, bleaching action (in-office).

- To evaluate the effects of complementary application of accelerators during bleaching therapy (heat, light or laser).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, either parallel, cross-over or split-mouth design.

Types of participants

Adults with discoloured teeth with any type of stain (due to chromatogenic agents, tetracycline, systemic fluoride intake, systemic diseases or patients dissatisfied with their current tooth colour). We will exclude studies assessing efficacy of whitening substances in extracted teeth.

Types of interventions

- Any tooth whitening product, with a chemical as opposed to abrasive mode of action, developed to be administered by a dental professional in the dental office. We will exclude studies comparing home-based products with those applied by a dental professional.
- Assisted bleaching, defined as an in-practice (professional) supplement to the home bleaching process.
- Complementary application of accelerators such as heat, light or laser.
- Comparison groups will be those receiving placebo or a different chemical whitening product, or an abrasive whitening product, or no whitening treatment.

Types of outcome measures

Primary outcomes

1. Patient satisfaction with the whitening procedure
2. Adverse effects (e.g. pulpitis, tooth sensitivity, gingival irritation)

Secondary outcomes

1. Digital readings of whiteness
2. Ordinal scales measuring whiteness

Search methods for identification of studies

For the identification of studies included or considered for this review, we will develop detailed search strategies for each database searched. These will be based on the search strategy developed for MEDLINE (see Appendix 1) but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules. There will be no restriction on language or date of publication.

The search strategy will combine the subject search with the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials in MEDLINE: sensitivity-maximizing version (2008 revision), as published in Box 6.4.c in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] (Higgins 2011).

Electronic searching

The following electronic databases will be searched.

- Cochrane Oral Health Group's Trials Register (to present)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* current issue) (see Appendix 3)
- MEDLINE via OVID (1948 to present) (see Appendix 1)
- EMBASE via OVID (1980 to present) (see Appendix 2)

Searching other sources

We will screen reference lists of included studies and relevant review articles identified by electronic searching in order to identify other potentially eligible articles. We will search online abstract indexes of the conference proceedings of the International Association for Dental Research (IADR) Annual Meeting (1991 to present) and the ProQuest Dissertation and Thesis database (1945 to present) for unpublished studies.

We will also search for unpublished studies in the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov.

Data collection and analysis

Selection of studies

Two review authors will, independently and in duplicate, screen the titles and abstracts of all records resulting from the searching process to identify potentially eligible studies. We will obtain full text copies of all eligible and potentially eligible studies, and two

review authors will assess the full text articles, independently and in duplicate, to determine whether or not they meet the inclusion criteria. Any studies deemed not to meet the inclusion criteria at this stage will be recorded in the 'Characteristics of excluded studies' table. Disagreements will be resolved by a third review author who will act as arbiter to make a decision in a team discussion. We will contact the authors of studies in the event that eligibility criteria or other important information is not clear.

Data extraction and management

To guarantee consistency in data extraction, we will pilot test a spreadsheet prior to the official data extraction process. Using a standardised data extraction form, two review authors will, independently and in duplicate, extract and tabulate data regarding study design, intervention(s) and comparison, characteristics, total numbers of participants randomised, allocated to each group, and analysed, duration of follow-up, outcomes measured and their definitions, and any other information considered relevant to this review. We will also record descriptive information about country, age, sex, participant selection criteria, sponsor, and declared conflict of interest.

Assessment of risk of bias in included studies

We will conduct the assessment of risk of bias of included studies using the Cochrane risk of bias tool, as described in Chapter 8 of the Cochrane Handbook (Higgins 2011). Two review authors will assess the risk of bias of all included studies independently and in duplicate. If disagreement occurs, it will be discussed and, if necessary, a third review author will act as arbiter to reach consensus. We will assess the following domains within each included study as either: low risk of bias, unclear risk of bias (either lack of information or uncertainty over the potential for bias) or high risk of bias.

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other potential sources of bias

We will present a 'Risk of bias graph' showing the proportion of studies with each of the judgements (low, unclear and high risk of bias) for each entry in the tool, and also a 'Risk of bias summary' figure cross-tabulating all of the judgements within each study. These assessments will be reported for each individual study in the 'Risk of bias' table within the section 'Characteristics of included studies'.

An overall assessment of risk of bias for an outcome across studies will be made to be incorporated into the judgements about the quality of evidence (confidence in the estimates) in the 'Summary of findings' tables (Schünemann 2011a). Since the primary outcomes are patient-reported, participant blinding will be essential for a study be at low risk of bias for the primary outcomes. For the secondary outcomes, blinded outcome assessors will be deemed to be essential for a study to be assessed at low risk of bias.

Study authors will be contacted for clarification if necessary.

Measures of treatment effect

For continuous outcomes (e.g. digital readings of whiteness, ordinal scales measuring whiteness, pain due to tooth sensitivity, and patient satisfaction), we will use mean difference (MD) and its 95% confidence interval for estimating treatment effect, when outcomes are reported in the same scale. If studies measured the same outcome but using different scales, we will calculate standardised mean difference (SMD) and their 95% confidence interval.

For dichotomous outcomes (e.g. adverse events measured as dichotomous), we will estimate treatment effect using risk ratio (RR) with 95% confidence interval. If the number of events is zero in a treatment arm of any of the included studies in a meta-analysis, we will consider peto odds ratio (OR) because it does not need corrections for zero cell counts when this fixed method is used (Deeks 2011).

Unit of analysis issues

We will combine data from parallel and split-mouth studies using the procedure described by Lesaffre et al (Lesaffre 2009) and Elbourne et al (Elbourne 2002). Since we anticipate that some split-mouth studies would not report the results based on a paired analysis, we will approximate it by imputing the pooled standard deviation from the standard deviations of the two groups using a correlation coefficient of 0.75 assumed a priori. This method uses a coefficient to describe how similar the measurements of the intervention in one side and on the other side are within a participant (Follmann 1992).

Assessment of heterogeneity

Since heterogeneity can be anticipated because of the regimen of application of whitening agents, we will assume that studies will be evaluating different but related intervention effects. Therefore, we will use a random-effects model for meta-analysis rather than a fixed-effect model. We will use the Chi^2 test to determine the presence of statistical heterogeneity, using a level of significance of 0.1. In order to estimate the percentage of total variation across the studies due to heterogeneity rather than chance, we will use the I^2 statistic, and its interpretation will be based on the recommendations reported in section 9.5 of the Cochrane Handbook (Deeks 2011).

Assessment of reporting biases

Assessment of reporting biases will be done following the recommendations of The Cochrane Collaboration (Sterne 2011). We will evaluate two types of reporting bias.

- We will search protocols of the included studies to check for outcome reporting bias.
- For outcomes in which meta-analysis is performed, and the number of studies is sufficient to assess reporting bias (i.e. at least 10 studies), we will use funnel plots to assess publication bias (Egger 1997).

Data synthesis

We will pool split-mouth, cross-over, and parallel studies in the same meta-analysis, estimating the standard error of the mean difference between the intervention and control side.
We will enter data into the Review Manager (RevMan) software to obtain the corresponding pooled estimate, and the generic inverse variance method will be used for this purpose (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

The two factors considered, a priori, for subgroup analysis as possible explanations for heterogeneity and its corresponding hypothesis are:

- different kind of reaction catalysts: the effect estimates will be different among these types of catalysts (temperature, light sources, lasers); and
- study design: split-mouth, cross-over and parallel group studies will be pooled as subgroups in the same meta-analysis. The effect estimates will be different among these types of study design.

When enough information from studies is available, we will only conduct subgroup analysis if heterogeneity is at least moderate, which corresponds to an I^2 statistic > 30%.

Sensitivity analysis

If any correlation coefficient between the two-side treatment outcome within a participant is required to be imputed for a split-mouth study, we will conduct a sensitivity analysis to estimate the robustness of the treatment effect on the current assumptions using 0.5, 0.75 and 0.9 coefficients. We will conduct a second analysis to determine the robustness of the results for studies at low overall risk of bias.

Summary of findings table

We will use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) rating system to evaluate the confidence in the effect estimates (quality of evidence) of the body of evidence, across outcomes (Guyatt 2008). In the GRADE approach, RCTs begin as high-quality evidence, but confidence in estimates decreases if serious limitations in study design (risk of bias), inconsistency, imprecision, indirectness, and/or publication bias is present (Schünemann 2011b). These assessments will be conducted independently and in duplicate. The 'Summary of findings' tables will be built using the GRADEProfiler software Version 3.5, © GRADE Working Group 2004-2007 (Brozek 2009; Schünemann 2011a).
The patient population to be included in the table will be adults with discoloured teeth with any type of stain. The table will summarise the quality of the evidence for both primary and secondary outcomes listed in the section 'Types of outcome measures':

1. patient satisfaction with the whitening procedure;
2. adverse effects (e.g. pulpitis, tooth sensitivity, gingival irritation);
3. digital readings of whiteness; and
4. ordinal scales measuring whiteness.

The comparison for this table will be between any type of tooth whitening product, with a chemical mode of action, developed to be administered by a dental professional in the dental office, against either placebo, or other whitening agents.
The criteria to determine which specific comparison to include in the table will be:

1. results regarding the higher number of outcomes listed above;
2. highest number of studies; and
3. highest number of patients.

These criteria will be used hierarchically.

ACKNOWLEDGEMENTS

We would like to thank those who took the time to peer review this protocol: Hana Hasson and Edward Lynch.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE via OVID search strategy

1. Tooth bleaching/
2. exp Tooth/
3. (tooth or teeth or dental or enamel).ti,ab.
4. or/2-3
5. Tooth bleaching agents/
6. Hydrogen peroxide/
7. (peroxide$ or carbamide$ or hexametaphosphate$).ti,ab.
8. (bleach$ or whiten$ or brighten$).ti,ab.
9. ((bleach$ or whiten$ or brighten$) and ("in-office$" or "in office$")).ti,ab.
10. ((bleach$ or whiten$ or brighten$) and (professionally-applied or "professionally applied")).ti,ab.

11. or/5-10
12. 4 and 11
13. 1 or 12

The above subject search will be linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] (Higgins 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 2. EMBASE via OVID search strategy

1. exp Tooth/
2. (tooth or teeth or dental or enamel).ti,ab.
3. 1 or 2
4. Bleaching agent/
5. Hydrogen peroxide/
6. (peroxide$ or carbamide$ or hexametaphosphate$).ti,ab.
7. (bleach$ or whiten$ or brighten$).ti,ab.
8. or/4-7
9. 3 and 8

The above subject search was linked to the Cochrane Oral Health Group filter for EMBASE via OVID:

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.
5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

Appendix 3. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

1. MeSH descriptor Tooth bleaching this term only
2. MeSH descriptor Tooth explode all trees
3. (tooth in Title, Abstract or Keywords or teeth in Title, Abstract or Keywords or dental in Title, Abstract or Keywords or enamel in Title, Abstract or Keywords)
4. (#2 or #3)
5. MeSH descriptor Tooth bleaching agents this term only
6. MeSH descriptor Hydrogen peroxide this term only
7. (peroxide* in Title, Abstract or Keywords or carbamide* in Title, Abstract or Keywords or hexametaphosphate* in Title, Abstract or Keywords)
8. (bleach* in Title, Abstract or Keywords or whiten* in Title, Abstract or Keywords or brighten* in Title, Abstract or Keywords)
9. (#5 or #6 or #7 or #8)
10. (#4 and #9)
11. (#1 or #10)

CONTRIBUTIONS OF AUTHORS

- Alonso Carrasco-Labra (AC) will be responsible for co-ordinating the review, and contacting authors of studies for additional information.
- Romina Brignardello-Petersen (RB) will be responsible for entering data into Revman.
- RB and AC will obtain full texts.
- AC and Ignacio Araya (IA) will be responsible for searching for studies. IA and AC will be also responsible for title and abstract screening.
- Nicolás Yanine (NY) and RB will be responsible for extracting data from studies.
- NY and AC will be responsible for full-text evaluation in order to assess inclusion in the review.
- Gabriel Rada (GR) will act as arbiter when disagreements occur. In addition, he will provide methodological support and carry out analysis with RB and AC.
- Graham Chadwick (GC) will provide clinical expert support

All review authors will contribute to analysing and interpreting data, and writing the final draft of the review.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- Universidad de Chile, Faculty of Dentistry, Chile.
- Pontificia Universidad Católica de Chile, Faculty of Medicine, Chile.

External sources

- Cochrane Oral Health Group Global Alliance, UK.

All reviews in the Cochrane Oral Health Group are supported by Global Alliance member organisations (British Orthodontic Society, UK; British Society of Paediatric Dentistry, UK; National Center for Dental Hygiene Research & Practice, USA and New York University College of Dentistry, USA) providing funding for the editorial process (http://ohg.cochrane.org).

- National Institute for Health Research (NIHR), UK.

All reviews in the Cochrane Oral Health Group are supported by NIHR Systematic Reviews Programme infrastructure funding.