Effectiveness of Dentist-Prescribed, Home-Applied Tooth Whitening, A Meta-analysis

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PRE-WHITENING

POST-WHITENING

Abstract

Introduction. Common clinical experience suggests that tooth whitening agents are 100% effective. This study uses meta-analysis of data from published randomized controlled clinical trials to determine the efficacy of tooth whitening agents.

Methods. A MEDLINE search strategy was developed and implemented to systematically identify clinical trials on dentist-prescribed, home-applied tooth whitening agents, using 10% carbamide peroxide, published between 1989-1999. Inclusion criteria (e.g., in English, human clinical trials) and exclusion criteria (e.g., not placebo controlled) were established and clinical trials that met these criteria were critically appraised for validity and clinical applicability. Meta-analysis was then used to quantitatively integrate the findings.

Results. Seven studies were identified that met the inclusion and validity criteria. These studies indicated that:

- Whitening results in a significant mean change of 6.4 shade guide units ($p < 0.01$), while the placebo control group exhibited little change (0.7 0.6, $p > 0.05$).
- 93% of the bleached patients exhibited 2 shade guide unit change, while 20% of the placebo control group exhibited this change.
- The brand of bleaching agent had a significant effect on tooth whitening, but the daily application time and duration of treatment did not.
- Whitening is maintained for 6 months for 1/2 of the people treated.
- Neither gingival indices nor plaque indices were adversely or favorably affected by bleaching.

Clinical Applicability. The data from the reviewed studies indicate that rather than being 100% effective, on average:

- 73% (93% for bleached group minus 20% placebo group) of people who whiten their teeth will exhibit a whitening that is 2 shade guide units greater than the placebo.
- 20% of the people who use dentist-prescribed, home-applied bleaching will achieve a mean whitening effect of 5 shade guide units.
- Re-treatment for 50% of people may be necessary to maintain this effect longer than 6 months.
- The methods used here are Internet applicable for other clinical topics.

Keywords: Tooth whitening, tooth bleaching, dental bleaching, tooth bleaching effectiveness

Introduction

Over the last decade, the demand for esthetic dentistry has grown tremendously as people seek to improve their smile. The introduction of the first paper on at-home tooth whitening by Haywood and Heymann¹ in 1989 helped to revolutionize esthetic dentistry.

With the increasing popularity and rapid development of bleaching agents, questions also arose concerning their efficacy, longevity, and safety. Since 1989 over 600 articles on tooth bleaching have been published. Numerous studies suggest the effectiveness of dental products using 3% hydrogen peroxide (10% carbamide peroxide) in whitening teeth.^{2,3} To achieve these benefits, bleaching agents are used for weeks at a time. Long-term use, however, increases the safety concerns that hydrogen peroxide containing agents may cause pulpal damage and/or gingival inflammation.^{4,5}

The American Dental Association responded to these concerns by releasing "Guidelines for the Acceptance of Peroxide-Containing Oral Hygiene products"⁶ in 1994. According to these Guidelines, clinical efficacy may be demonstrated by a change of two value-oriented shade increments. A perceptible color change should be maintained in 50% of the recall population at 6 months as compared to the control to reflect duration of efficacy.

In this study, we systematically reviewed the published literature on dentist-prescribed, home-applied tooth whitening agents to assess the efficacy and safety of this procedure. In particular we were interested in capturing this information in a quantitative way that can be conveyed to the patient.

Materials and Methods

Information Retrieval

A MEDLINE search strategy was developed to include the years 1989-1999 inclusive (Table 1), and implemented on the PubMed interface for MEDLINE at the US National Library of Medicine (<http://www.ncbi.nlm.nih.gov/PubMed/>). The search strategy was based on the recommendations of the US Agency for Health Care Policy and Research⁷ and the Centre for Evidence-based Medicine (<http://cebm.jr2.ox.ac.uk/docs/levels.html>) for establishing levels of evidence for quality.

Table 1. PubMed Search Strategy for Tooth Bleaching*

Step #	Term
1	Tooth Bleaching
2	Limit 1 to English
3	Limit 2 to human
4	Limit 3 to randomized controlled trials
5	Limit 4 to 1989 - 1999

* The search can be rerun at the reader's convenience at PubMed in one of two ways:

1. Access PubMed at the Internet uniform resource locator:
<http://www.ncbi.nlm.nih.gov/PubMed/> Then, copy and paste the following in the box "Search PubMed for _____":

((((("tooth bleaching"[MeSH Terms] OR tooth bleaching[Text Word]) AND Randomized Controlled Trial[ptyp]) AND English[Lang]) AND notpubref[sb]) AND "human"[MeSH Terms]) AND ("1989"[PDat] : "2001"[PDat]))
2. Click on the Internet uniform resource locator (URL) on the following page, or copy and paste into the computer Internet URL box.

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=%28%28%28%28%28%28%22tooth%20bleaching%22%5BMeSH%20Terms%5D%20OR%20tooth%20bleaching%5BText%20Word%5D%29%20AND%20Randomized%20Controlled%20Trial%5Bptyp%5D%29%20AND%20English%5BLanguage%5D%29%20AND%20notpubref%5Bsb%5D%29%20AND%20%22human%22%5BMeSH%20Terms%5D%29%20AND%20%28%221989%22%5BPDat%5D%20%3A%20%222001%22%5BPDatt%5D%29%29

Eligibility Criteria

Identified studies were reviewed for exclusion/inclusion using the following criteria:

1. Clinical, not laboratory trial,
2. Placebo control,
3. 10% carbamide peroxide active ingredient,
4. Application using a custom-fitted tray,
5. Outcome variables reporting efficacy, or color whitening, using a change in shade guide units, and
6. Gingival and plaque indices to reflect safety.

Excluded randomized control articles are indicated in Table 2a and excluded clinical trials in Table 2b.

Table 2a. Excluded randomized controlled trials, and reason for exclusion

Author	In vivo Human Trial	Placebo Control	Patient Applied Tray
Crim GA, 1992	No		
Fischman SL, <i>et al.</i> , 1992			No
Heymann, HO, <i>et al.</i> , 1998	No		
Hansen-Bayless, <i>et al.</i> , 1992	No		
Kowitz GM, <i>et al.</i> , 1994		No	
Kozlovsky A, <i>et al.</i> , 1996			No
Kugel CM, <i>et al.</i> , 1997			No
Matis, BA, <i>et al.</i> , 1999		No	
Miles PG, <i>et al.</i> , 1994	No		
Nathoo SA, <i>et al.</i> , 1994		No	
Schulte JR, <i>et al.</i> , 1993		No	
Schulte JR, <i>et al.</i> , 1994		No	
Whitman FJ, <i>et al.</i> , 1995			No

Table 2b. Excluded clinical trials, and reason for exclusion

Author(s)	10% Carbamide Peroxide	Placebo Control	Tetracycline Stained Teeth	Patient Applied Tray	Shade Guide
Lyons, 1998		No			
Haywood, 1997			Yes		
Swift, 1997				No	
Curtis, 1995		No			
Sterrett, 1995					No
Haywood, 1994		No			
Small, 1994		No			
Rustogi, 1994					No
Toh, 1993	No				
Haywood, 1993					No
Gegauff, 1993					No
Ouellet, 1992		No			
Rosenstiel, 1991					No

Critical Appraisal

To determine the validity of the identified studies, we employed the 7 criteria used on the Critical Appraisal Worksheets proposed by the Centre for

Evidence-based Medicine (<http://cebmr2.ox.ac.uk/docs/teachingresources.html>)⁸ (Table 3).

Table 3. Validity Assessment*

Issue	Yes/No
1. Was the assignment of patients to treatments randomized? 2. Was the randomization list concealed? 3. Were all patients who entered the trial accounted for at its conclusion? 4. Were they analyzed in the groups to which they were randomized? 5. Were patients and clinicians kept "blind" to which treatment was being received? 6. Aside from the experimental treatment, were the groups treated equally? 7. Were the groups similar at the start of the trial?	
* http://cebmr2.ox.ac.uk/docs/teachingresources.html	

Articles meeting 5 out of 7 validity criteria were included (Table 4). The results of these studies

were extracted for further analysis (Table 5).

Table 4. Validity Assessment, Included Articles

Author(s)	Validity Criteria*						
	1	2	3**	4	5**	6	7
Curtis, et al., 1996	Y	NS	Y (58/52)	Y	Y (D)	Y	NS
Howard, 1992	Y	NS	Y (37/32)	Y	Y (D)	Y	NS
Kowitz, et al., 1994	Y	NS	Y (75/70)	Y	Y (D)	N	NS
Matis, et al., 1998	Y	Y	Y (60/60)	Y	Y (D)	Y	Y
Reinhardt, et al., 1993	Y	NS	Y (56/56)	Y	Y (D)	Y	NS
Rosentiel, et al., 1996	Y	NS	Y (52/?)	Y	Y (D)	Y	Y
Russell, et al., 1996	Y	Y	Y (50/50)	Y	Y (D)	Y	Y
* Y=Yes; N=No; NS=Not Stated ** # Subjects at start / # subjects end *** D=double blind; S=single-blind							

Table 5. Studies and variables included in the meta-analysis

Author(s)	Bleaching Products (Brand)**	Ct	Sample Size			Treatment (time/day)	Time (days)	Follow-up (weeks)	Outcome Variable(s)
			Exp 1	Exp 2	Exp 3				
Curtis, et al., 1996	5	3030		N/A	N/A	Overnight	>14	1,2,6	
Howard, 1992	1,2	8	12	12	N/A	<4hr/day	<7	6	Gingival Index, Plaque Index
Kowitz, et al., 1994	2,4	22	24	24	N/A	<4hr/day	>14	1,2	Shade Guide
Matis, et al, 1998	5	3030		N/A	N/A	Overnight	>14	1,2,3,6, 12,24	Shade Guide
Reinhardt, et al, 1993	1,2,3	16	15	17	16	<4hr/day, Overnight	>14	3	Shade Guide, Gingival Index, Plaque Index
Rosentiel, et al, 1996	5	26	26	N/A	N/A	Overnight	<7	1,3,6, 12,24	Gingival Index
Russell, et al, 1996	5	26	24	N/A	N/A	Overnight	>14	1,2,6, 12,24	Shade Guide
* # = number of patients, Ct = control group, Exp = experimental group ** 1 = White & Brite, Omni International 2 = Rembrandt Lighten, Den-Mat 3 = Proxigel, Reed and McCormick 4 = Colgate Platinum, Colgate Palmolive 5 = Opalescence, Ultradent Products, Inc.									

Statistical Methods

We evaluated shade guide unit change to reflect efficacy and both gingival and plaque indices to reflect safety. All three were analyzed for the

significance of four variables: treatment group, daily application time, the duration of treatment, and brand of bleach (Table 6).

Table 6. Overview of Meta-analysis Variables

Using the computer program SPSS, the treatment groups and daily application time were analyzed using the t-test (Table 7a, b).

Analysis of variance (ANOVA) was performed to isolate differences in effectiveness between the 3 different duration of treatment lengths (1, 2, and 3 weeks, Table 7c) as well as between the

5 different brands of bleaching agents used (Table 7d).

To determine the size and potential benefit of tooth bleaching from a patient-centered perspective, we calculated the % of patients affected and the mean number needed to treat (NNT) (Table 8) <http://cebm.jr2.ox.ac.uk/docs/nnt.html>).

Table 7a. Mean change in shade guide units

Variable	Group	Mean	SD*	N**	Min	Max	p-value
Treatment Group	Active	5.9	4.094		0.4	17.5	<0.01
	Control	0.7	0.6	174	0	1.5	

Table 7b. Mean change in shade guide units by treatment time

Variable	Group	Mean	SD*	N**	Min	Max	p-value
Daily Application Time	<4 hr/day	4.6	2.1	97	0.4	7.1	>0.2
	Overnight	7.8	5.5	77	4.5	17.5	

Table 7c. Mean change in shade guide units by treatment duration

Variable	Group	Mean	SD*	N**	Min	Max	p-value
Duration of Treatment	1 week	4.9	1.6	24	3.7	6	>0.2
	2 weeks	8.7	5.9	102	5.1	17.5	
	3 weeks	4.4	2.2	48	0.4	6.9	

Table 7d. Mean change in shade guide units by bleach brand

Variable	Group	Mean	SD*	N**	Min	Max	p-value
Brand of Bleach	Opalescence	11.4	8.6	54	5.3	17.5	<0.01
	Colgate Platinum	7.1	NA	24	NA	NA	
	Rembrandt	5.3	1.3	52	3.7	6.9	
	Proxigel	4.7	0.21	17	4.6	4.9	
	White & Brite	3.6	2.1	27	0.4	6	

* Standard Deviation, ** N = Number of Subjects

Table 8. Number needed to treat to achieve 2 shade increment benefit

Author	Product	Control Event Rate CER	Experimental Event Rate EER	Absolute Benefit Increase (EER-CER)= ABI	Number Needed to Treat (1/ABI) x 100= NNT
Kowitz et al, 1994	Rembrandt	22.7%	90.9%	68.2%	1.5
Kowitz et al, 1994	Colgate	22.7%	100%	77.3%	1.3
Russell et al, 1996	Opalescence	15.4%	87.5%	72.1%	1.4

Because all people do not respond similarly, NNT provides a patient centered outcome estimate. The NNT identifies how many people need to be treated for one patient to obtain a significant benefit when compared to the control. We determined an observable benefit in two ways:

1. a two-increment change in shade guide units and
2. a mean change in total shade guide units.

Results

The MEDLINE search (Table 1) identified 28 randomized controlled trials evaluating tooth bleaching. Of these, 20 examined dentist-prescribed, patient applied tooth whitening agents. Of the 20, 13 did not meet additional inclusion criteria (Table 2). The 7 remaining studies were critically appraised and met validity criteria (Tables 3, 4).

Critical Appraisal of Clinic Importance

Of the 7 studies, 5 studies evaluated efficacy using shade guide units, while 3 examined gingival index and or plaque index (Table 5). The data in these studies indicated that dentist-prescribed, home-applied agents using a 10% carbamide peroxide gel delivered in a custom-fitted tray whitened teeth significantly, when compared to a placebo control group (Figure 1 Table 7a). The bleached group had a significant mean change of 5.9 (SD = $\pm$ 4) shade guide units out of a possible 24 (24% change; $p < 0.01$), while the control group had a mean change of 0.7 (SD = $\pm$ 0.6) shade guide units (3% change; $p > 0.05$).

Neither daily application time nor duration of treatment had a significant effect on the change in mean shade guide units (Table 7b, 7c). Daily application time was categorized into two groups who wore bleaching trays either (1) less than 4 hours/day or (2) overnight. Mean changes in shade guide units changes were 4.6 (SD = $\pm$ 2.1) and 7.8 (SD = $\pm$ 5.5), respectively. While the change was greater with longer wear, the statistical difference was not significant (Table 7b, $p > 0.2$).

Duration of treatment ranged from one to three weeks. Mean changes in shade guide units were 4.9 (SD = $\pm$ 1.6), 8.8 (SD = $\pm$ 5.9), and 4.4 (SD = $\pm$ 2.2) for 1 week, 2 weeks, and 3 week long treatments, respectively. Despite the extended exposure time to the active bleaching ingredient, no statistical differences were noted (Table 7c, $p > 0.2$).

Lastly, in determining efficacy, the five brands of bleaching agents were compared for effect on the mean change in shade guide units (Figure 2 Table 7d). Opalescence produced a significantly

greater mean change in shade guide units than three of the other brands (mean = 11.4 8.6, $p = 0.01$). The 4th brand was not included in this comparison since the reported data were insufficient for analysis.

Clinical Applicability

To quantify the bleaching experience from a patient's perspective, we calculated the % of people that would achieve the indicated results and from that a number needed to treat (NNT). That is, the number of people that would need to be treated for one person to show a whitening that was significantly greater than the control group. This calculation was done for two outcome variables: (1) percentage of people with a two-increment change in shade guide units and (2) mean shade guide change.

The percentage of people who will achieve 2 shade guide unit change, when compared to the control group was 73% (Table 8).

This translates to an NNT of 1.4. Stated another way, 1.4 people will be treated for 1 to achieve a 2-unit shade guide change that is greater than the control. After rounding, this is equivalent to approximately 2 out of 3 people (i.e., 66% 73%).

Using similar methods, the percent of people who will achieve a shade guide change of 5 units greater than the control is 20%. This translates to an NNT of 5. Thus, for every 5 people treated, 1 will achieve a shade guide change of 5 units greater than the control.

Finally, using similar methods, at 6 months 50% of the people who achieved a shade guide change of 2 maintained that shade guide change, while the other 50% did not.

Safety

To assess the safety of 10% carbamide peroxide gel, the identified studies examined plaque accumulation and gingival inflammation. For the plaque index (PI), there were no significant differences between the bleached and control groups PI (Table 9, all $p > 0.3$).

Table 9. Mean change in plaque indices

Variable	Group	Mean	SD*	N**	Min	Max	p-value
Treatment Group	Active	0.45	0.28	73	0.1	0.8	0.5
	Control	0.29	0.44	35	0	0.8	
Daily Application Time	<4 hr/day	0.47	0.35	25	0.2	0.8	0.9
	Overnight	0.43	0.28	48	0.1	0.8	
Duration of Treatment	2 weeks	0.12	0	25	0.1	0.1	0.3
	3 weeks	0.5	0.27	48	0.1	0.8	
* Standard Deviation, ** N = Number of Subjects							

Table 10. Mean change in gingival indices

Variable	Group	Mean	SD*	N**	Min	Max	p-value
Treatment	Active	0.25	0.15	129	0	0.5	0.3
Group	Control	0.16	0.15	64	0	0.4	
Daily	<4 hr/day	0.23	0.21	25	0	0.4	0.8
Application Time	Overnight	0.26	0.13	104	0.08	0.5	
Duration of Treatment	1 week	0.3	n/a	26	0.3	0.3	0.9
	2 weeks	0.28	0.28	55	0.09	0.5	
	3 weeks	0.23	0.14	48	0	0.4	

* Standard Deviation, ** N = Number of Subjects

Three studies determined the difference in gingival index (GI) between baseline and the end of treatment (Table 10). There were no significant differences between the bleached and control group's GI for the three treatment differences: treatment group, daily application time, and duration of treatment on the mean change of GI (all $p > 0.3$).

Discussion

This study was conducted to determine the efficacy of tooth whitening agents and quantify the whitening from a patient's perspective using a meta-analysis of data from published human clinical trials.

According to the ADA's "Guidelines for the Acceptance of Peroxide-Containing Oral Hygiene products"⁶ four outcomes are recommended to evaluate tooth bleaching efficacy: shade guide, photography, colorimetry, and computer digitization. Only one of the identified studies reported photography results²² and none used computer digitization. Although a computerized colorimeter is objective and eliminates the potential for human bias and variability³, its clinical relevance is unclear.

The meta-analysis of the published clinical trials indicate that, in the patient populations examined, and for the whitening agents examined, tooth whitening is effective and it neither adversely or favorably affects the gingiva or plaque. There are, however, several refinements to this statement. First, contrary to expectation, 73%, not 100% of the patients who undergo tooth whitening, can expect a shade guide change of 2

units. Second, 20% of patients can expect a 5-shade guide unit change. Finally, the current formulations of carbamide peroxide gel are not equally effective, thus some products are more significantly more efficacious than others are.

The complexities of these subtleties are, perhaps, best understood in the context of Figure 1.

Figure 1.

Comparison of placebo gel and bleaching gel in effecting tooth color change. The square indicates the mean change in shade guide color. The vertical bars indicate the standard deviation.

Figure 1 indicates the mean change in shade guide units is ~ 5. If this were interpreted as the occurrence in most patients, a clinician might suggest, inaccurately, that "on average a patient can expect a 5 shade guide unit change." In fact, the data when calculated as the NNT suggest

less than half this effect, as indicated in the previous paragraph. For patient communication, the NNT thus offers an alternate, more nuanced method for managing a patient's expectation of care outcomes. On the other hand, it is also clear there are significant differences in product performance (Figure 2).

Figure 2.

Comparison of 5 different bleaching gels in effecting tooth color change. The square indicates the mean change in shade guide color. The vertical bars indicate the standard deviation.

This can also be used in guiding product selection and recommendations.

Another aspect of this study was the use of the Internet to carry out the initial elements of the review. These elements point toward newer methods of clinical information access and retrieval. With open access to PubMed (<http://www.ncbi.nlm.nih.gov/PubMed/>), clinicians can now routinely and inexpensively run clinical searches to obtain the most current information. Using PubMed's "Limits" function, as used in this study stratifies the level of evidence. Alternatively the use of PubMed's "Clinical Queries" (<http://www.ncbi.nlm.nih.gov/80/entrez/query/static/clinical.html>) allows one to prepare sensitive or specific clinical searches on etiology, diagnosis, therapy, or prognosis. Finally, the PubMed's "cubbys" (<http://www.ncbi.nlm.nih.gov/80/entrez/cubby/login.fcgi?call=so.SignOn..Login>) provide a mechanism for both saving and retrieving searches. Saved searches can then be re-run to update the information ad libitum. Accessing information beyond the title and abstract are also facilitated by PubMed. Articles that are not available in a personal or local library can be ordered through PubMed's "Loansome Doc" service (<http://tendon.nlm.nih.gov/ld/loansome.html>). This approach to accessing key clinical information offers one a low cost, low barrier mechanism for clinical updating.

Discussion

Several caveats regarding the results also need to be addressed. First, the identified studies utilized two shade guide systems: Trubyte Bioform (Densply/York Division) and the Vita shade guide (Lumin Vacuum Shade Guide, Via Zahnfabrik, H. Rauter GmbH & Co. KG, Sackingen, Germany) for shade matching. Utilizing a shade guide system to measure efficacy has the following limitations:

1. There is no shade guide standard.
2. The shade guide units are not evenly distributed in color space and are not as discriminating as the measured colorimeter parameters.³
3. Color matching using a shade guide is subject to clinician variability and bias.

Despite these limitations, measuring color change with a shade guide remains the most clinically relevant patient-centered outcome measure. To accommodate for these different standards, changes were noted as % change and NNT calculated. A second caveat is the limiting of this systematic review to randomized controlled trials identified on MEDLINE, published in English. The disadvantages of these choices are they eliminate from consideration clinical trials that are cohort, case-control, and/or case series. They also eliminate articles that might appear in other databases (e.g., EMBASE, Cochrane) but not MEDLINE, and in other languages. The advantage, however, is that randomized controlled trials provide the strongest level of evidence.^{7,8}

(<http://cebm.jr2.ox.ac.uk/docs/levels.html>), MEDLINE is the world's largest free access medical literature database, and the cited articles will be largely available to an English speaking audience. Third, the review does not address publication bias. That is, those articles that are not published because they did not show clinical efficacy cannot be evaluated. Thus, this review itself is biased, in that it may overestimate clinical efficacy. In summary, given several caveats, the results indicate that, on average, dentist-prescribed, home-applied tooth whitening will whiten teeth and neither adversely or beneficially affect the gingiva or plaque.

Case Studies

Case 1. Tooth Whitening

A 40-year-old female presented with a chief complaint: "I want my teeth whitened." The patient's pretreatment shade was A4 (left). After 2 weeks of bleaching a shade of B1 was achieved (right).

Figure 1a. Before bleaching.

Figure 1b. After bleaching.

Case 2. Tooth Whitening + Removable Partial Denture

A 51-year-old Hispanic female presented with a chief complaint of an ill-fitting maxillary removable partial denture (RPD) that was several years old. The patient was also unhappy with the esthetics and color (left). In conjunction with RPD fabrication, bleaching was prescribed (right).

Figure 2a. Before bleaching.

Figure 2b. After bleaching.

Figure 3a. Before treatment.

Figure 3b. After treatment.

Case 3. Tooth Whitening + All Ceramic Crowns

A 49-year-old female presented with a chief complaint of unesthetic maxillary lateral incisor porcelain fused to metal crowns. The patient reported having the crowns fabricated 15 years previously to cover "peg laterals." Her teeth were now much darker (A3) than her crowns, and metal margins were exposed on the crowns (left). Treatment included tooth whitening, gingival recontouring, and new all-ceramic crowns to match the new tooth shade (C1) (right).

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