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Randomized Controlled Trials on Tooth Whitening: Evidence from International Research

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Randomized Controlled Trials on Tooth Whitening: Evidence from International Research

Considerations on tooth whitening worldwide

The dramatic growth and impact of tooth whitening worldwide has raised patients' awareness of the appearance of their smile. The introduction of whitening strips in 2000 played an appreciable role, expanding access to an increasingly broad population. Some seven years later, these strips remain one of the most popular options for initial esthetic dentistry.

There is considerable published evidence on the safety and efficacy of whitening strips, including prominent clinical trials. One enabling factor was the advent of digital image analysis, an objective instrumental method for measuring *in vivo* color change. Used in a rigorous clinical program with appropriate experimental controls, this research provides significant evidence on clinical response to tooth whitening with strips or other delivery systems.

This special issue of the *American Journal of Dentistry* highlights the global aspects of clinical research on tooth whitening, presenting technical and clinical data pertaining to tooth whitening, using digital imaging. The research comes from widely differing settings, ranging from research hospitals to private practice, in distinct populations and cultures across the globe.

This special issue of the *American Journal of Dentistry* represents one of the largest collections of global clinical research on peroxide tooth whitening. The randomized controlled trials described herein support the whitening action of Crest Whitestrips in the absolute and relative to various experimental controls. Such diverse testing, with respect to populations, sites and controls, provides important evidence of the merits of the method (digital image analysis) and treatment (hydrogen peroxide whitening strips).

We hope you will find these papers interesting and educational. The *Journal* thanks Procter & Gamble, the manufacturer of Crest Whitestrips, for sponsoring this special issue.

Franklin García-Godoy, DDS, MS
Editor

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Tooth whitening clinical trials: A global perspective

ROBERT W. GERLACH, DDS, MPH

ABSTRACT: Tooth whitening has been the subject of extensive clinical trials research since the introduction of the first hydrogen-peroxide whitening strips in 2000. Availability of digital image analysis, an unambiguous and reproducible method for assessing color change, has contributed to global clinical research and product development on whitening strips. The research has included a series of global randomized controlled trials in distinct sites and cultures, involving 6-6.5% hydrogen peroxide whitening strips used for 7-21 days. These studies, conducted at research hospitals, dental schools, and private dental practice, demonstrated significant color improvement with whitening strips relative to baseline and/or various controls without serious adverse events. This integrated clinical trials research provides important evidence of long-term safety and effectiveness of tooth whitening with 6-6.5% hydrogen peroxide whitening strips. (*Am J Dent* 2007;20:3A-6A).

CLINICAL SIGNIFICANCE: Randomized controlled trials, conducted in diverse populations worldwide, provide evidence of initial tooth color improvement, post-treatment color stability, and extended safety for peroxide-containing whitening strips.

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Introduction

Tooth whitening is often the earliest patient introduction to esthetic dentistry. Treatment may be undertaken in-office or at-home using various professionally-applied or professionally-dispensed agents, or one of the self-directed whitening systems.[1] While individual techniques differ with respect to peroxide source, delivery, and other factors, the most prominent approaches rely on common oxidative chemistry, wherein peroxide diffuses from some bleaching gel into enamel. Whitening may be visually perceived and measured within a few days or weeks, depending on the technique used for peroxide delivery and retention, and the method of assessment.[2]

Peroxides have been used in various dental applications for more than a century, including infection control, periodontal therapy, and others.[3] Tooth whitening applications have drawn considerable research and development focus over the past three decades. Clinical trials have played a prominent role in these initiatives, with two milestones being particularly noteworthy. The first milestone came in 1989, when clinical research demonstrated the safety and efficacy of whitening with 10% carbamide peroxide delivered overnight in a custom bite splint tray.[4] This research and other exemplary clinical trials contributed to "nightguard vital bleaching" becoming the first popular approach for tooth whitening.[5,6] Clinical trials also played a limited role in expanding use of higher concentrations of carbamide peroxide in custom trays (15% or higher) for the purposes of faster whitening.[7,8] The second milestone came in 2000, with the publication of clinical research on flexible, hydrogen peroxide whitening strips.[9] Subsequent clinical research on whitening strips established the efficacy and safety of strip-based whitening at hydrogen peroxide concentrations ranging from 6-14%.[10-13] Initially characterized as paradigm-shifting, clinical trials on whitening strips expanded access and use, with strip-based whitening emerging as a predominant approach for intensive tooth whitening.[14]

Other peroxide whitening systems have been introduced, including barrier-free paint-on gels, rinses, and others. To date, evidence on these alternatives is limited, and none have yet achieved similar milestone successes as the custom tray or strip systems.[15,16] For the barrier systems (tray and strip), there is considerable and accumulating evidence on the tooth whitening safety and efficacy. Several reviews have assessed the evidence for tray-based whitening with carbamide peroxide or strip-based whitening with hydrogen peroxide.[1,6,17-19] Recently, a systematic review from the Cochrane Collaboration examined the quality of the evidence across delivery systems.[20] Using standard methods, the authors identified 25 randomized clinical trials that satisfied specific inclusion criteria. The search targeted randomized and controlled 14-day clinical trials using shade (tabs) or non-directional composite color (ΔE) as endpoints. Another 35 published clinical trials were excluded from the analysis.

The limitations of the systematic review process are apparent. In general, systematic reviews are limited to the published literature, and as such, may over-represent earlier paradigms, and downplay the most contemporary research. Publication bias may also be problematic with respect to negative findings and repetitive positive findings. Each systematic review has certain specific limitations as well, with relevance based on the appropriateness of the research question. For example, this recent review of home-use tooth whitening included only those clinical trials with a 14-day endpoint.[20] Shorter and longer studies (or products with shorter or longer labeled usage) were excluded. The research was further limited to studies involving conventional shade guides or the non-directional color measure ΔE, two endpoints with questionable pedigrees.[21-23]

Despite these possible limitations, systematic review represents one of the most prominent approaches to assess the strength of the evidence supporting specific healthcare practices. The recent Cochrane review of tooth whitening was comparatively robust, involving 25 clinical trials. This represented more evidence than many other recent systematic

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Fig. 1. Examples of global whitening strip products: **A.** USA, **B.** Mexico, **C.** Italy, **D.** Germany, **E.** China, **F.** France.

reviews involving popular adult oral care treatments. Completed reviews on occlusal adjustment, scaling and root planing, and guided tissue had 6, 8, and 17 clinical trials, respectively.[24-26] Other Cochrane adult oral care reviews involved even fewer clinical trials. One superficial conclusion is that there is considerable externally-reviewed clinical trials evidence on tooth whitening, at least for a few specific products. While the first clinical study was not published until 2000, whitening strips were most represented in the Cochrane review, accounting for 40% of all included research.[20] From this literature, the reviewers concluded that tooth whitening was safe and effective under labeled conditions of use, that there were significant differences between certain test products, and that tooth sensitivity and oral irritation represented the most common side effects associated with treatment. The reviewers also identified two areas as warranting additional research attention: diversity and longer term follow-up. Although planned independently of and prior to the Cochrane publication, this supplement to the *American Journal of Dentistry* was specifically intended to address end-of-treatment and post-treatment outcomes following testing in diverse settings, relative to global use of whitening strips (Fig. 1).

Technology assessment

The randomized controlled trial (RCT) is widely recognized as providing important biomedical evidence of efficacy and safety. A total of five RCTs are described in this special issue. All studies evaluated 6-6.5% hydrogen peroxide whitening strips. The individual strips held approximately 9-13 mg of hydrogen peroxide, depending on the concentration and arch.[27,28] Strip application was twice daily for 30 minutes, with treatment duration varying based on the objective of the individual clinical study. Comparisons were made to various positive and negative experimental controls including placebo. The research involved different populations and research teams in Europe, Asia and the Americas. All studies used common methods to assess safety and efficacy, following pharmaceutical research practices.

This diverse yet integrated research was possible, in part, because of the availability of a standard method for assessing color change (or the absence thereof) following different treatments. The RCTs reported herein all used a common, objective and instrumental method to assess efficacy, made possible by advances in digital camera technology and software analysis. In the first research paper, Sagel & Gerlach[29] describe the method – digital image analysis – in explicit detail *via in vitro* and *in vivo* studies on color measurement reproducibility. Laboratory reproducibility was assessed from serial measurements of tooth-shaped shade tabs collected on 2 consecutive days, while clinical reproducibility was assessed in a similar fashion from tooth color measurements on 14 healthy adult volunteers. Both the *in vitro* and *in vivo* experiments showed exceptional reproducibility, with intra-class correlation coefficients exceeding 0.99 in the laboratory study, and 0.97 in the more complex and relevant clinical study. This level of reproducibility, the authors concluded, supported use of the digital image analysis to generate consistent measurements of tooth color in diverse settings, regardless of the investigator, center or geography.

Previous research has described the application of digital image analysis in tooth whitening clinical trials, where it reportedly offers advantages with respect to objectivity, standardization, and quantification, while yielding archival data for quality assurance and secondary analysis. The method is reported to have particular merit in limiting bias in comparative research involving dissimilar delivery systems or studies involving negative experimental controls where treatment effects are visually evident and profound. Each of the five RCTs in this special issue involved dissimilar delivery systems (strip *versus* tray), and/or non-peroxide controls (placebo or dentifrice). One additional advantage, especially for inter-

Fig. 2. Digital image analysis equipment prepared for shipment to test site.

national research as described in this special issue, is that the entire measurement system can be easily transported virtually anywhere in the world and maintained for use in long-term clinical research (Fig. 2).

Two of the RCTs directly compared whitening strips to one other treatment group. Hernández Guerrero *et al*[30] reported a study from Mexico involving university students, a classic subject population with clinical trials conducted in dental schools. This randomized, double-blind study compared professional 6.5% hydrogen peroxide whitening strips and placebo strips over 3 weeks of use.[30] In addition to the safety outcomes, this RCT from Mexico provides important evidence of method validity, with digital imaging showing appreciable color improvement in the peroxide group, with little to no "placebo" whitening response. While placebo-controlled trials provide important evidence of absolute response, positive-controlled trials illustrate the magnitude of the response. Ferrari *et al*[31] reported on a positive-controlled study in Italy comparing 6% hydrogen peroxide whitening strips and daytime use of a marketed 10% carbamide peroxide custom tray system. This RCT, which was conducted in a dental practice with volunteer patients as study subjects, demonstrates the feasibility of using objective and instrumental digital imaging to assess tooth whitening in alternate settings.

Three of the RCTs compared whitening strips to multiple treatment groups. Bizhang *et al*[32] reported on digital image analysis in an extended, 18-month RCT. Subjects were randomly assigned 6% hydrogen peroxide whitening strips, 19% sodium percarbonate brush-applied gel that dries as a film, or placebo brush-applied gel without peroxide. In addition to the long-term safety outcomes, this study established the feasibility of using digital image analysis for extended clinical evaluation. Xu *et al*[33] reported on another complex clinical trial from China, where adults were randomized to 6% hydrogen peroxide whitening strips, a barrier-free 5.9% hydrogen peroxide paint-on gel, or water rinse which served as a negative experimental control. This RCT illustrates the importance of a barrier and not just starting concentration of peroxide on response. Despite similarities in starting concentration (~6% hydrogen peroxide), the strip and paint-on gel differed significantly ($P < 0.0001$) on improvement in yellowness, brightness, and redness, as well as overall color improvement,

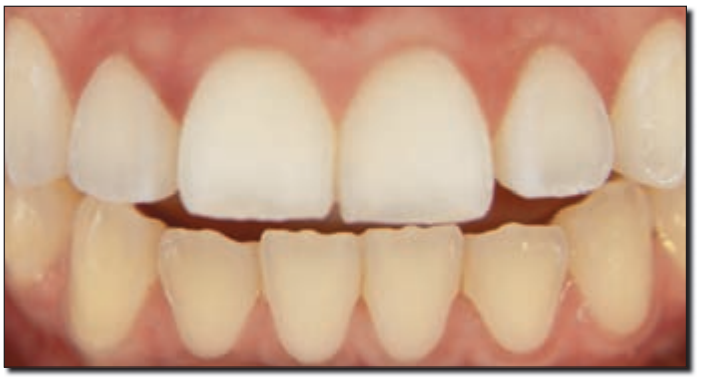

Fig. 3. Whitening strips after 21 days, maxillary arch treated (Mexico City study).

with these differences achieved with one-half the treatment duration (7 *versus* 14 days) for strips compared to the paint-on gel. Yudhira *et al*[34] reported on a 12-week comparison of 6% hydrogen peroxide whitening strips and two whitening dentifrices without peroxide. Using a so-called "double dummy" design, subjects received either peroxide or placebo strips for 2 weeks, and dentifrice (whitening or regular) for 12 weeks. Compared to the whitening dentifrices, the peroxide strip group had significant ($P < 0.0001$) whitening, and no significant ($P > 0.64$) post-treatment color degradation through 12 weeks.

Summary

This special issue of the *American Journal of Dentistry* represents perhaps one of the largest common collections of global clinical research on tooth whitening. Each of the five randomized controlled trials involved different populations, controls, and research teams. The study sites ranged from a research hospital to a private dental practice, in five distinctly different cultural settings. Each RCT received appropriate institutional ethical review prior to initiation, and overall, 243 individuals provided informed consent to study participation. Ages across the five RCTs ranged from 18-60 years, 71% of study subjects were female, and the population was, of course, quite diverse with respect to ethnicity. Overall, the research involved five different peroxide-containing products and five non-peroxide controls. Duration for the RCTs ranged from 2 weeks to 18 months, with three studies explicitly evaluating post-treatment color stability.

A common, unbiased and reproducible instrumental method was used to measure whitening response in these clinical trials. Each study showed significant ($P < 0.05$) tooth color improvement with 6-6.5% hydrogen peroxide whitening strips relative to baseline and to the various experimental controls. Individual study means were consistent with expectations, given these between-study differences in peroxide concentration, treatment duration, population age and starting tooth color, factors previously shown to affect whitening response.[1,35] In these five studies, as elsewhere, the greatest whitening occurred following use of the highest peroxide concentration strips for the longest duration in a younger population with considerable tooth discoloration at baseline (Fig. 3). Of note, the method – digital image analysis – was sufficiently robust to show temporal and barrier effects for various peroxide-containing products, without appreciable "placebo-response" in the various negative controls, across diverse research sites and over time.

One legacy for Whitestrips since the US launch in 2000 is

the dramatic increase in access to and utilization of tooth whitening. Where available, these easy-to-use whitening strips have provided an initial esthetic dentistry option to a broad range of individuals, irrespective of their socioeconomic strata. The new research further extends the evidence to include global applications. In all studies, the barrier-based hydrogen peroxide whitening strips yielded significant color improvement within a short time period (7-21 days) in dissimilar geographies and cultures, with differing diets, behaviors, and oral health practices. Strip whitening was durable, with more than 80% of initial color improvement still evident 18-months post-treatment. This whitening was achieved safely at-home. Minor tooth sensitivity and oral irritation were the most common adverse events, all of which resolved during treatment or post-treatment monitoring. In composite, this integrated research provides important long-term evidence of the global safety and effectiveness of tooth whitening with hydrogen peroxide whitening strips, and establishes strip-based tooth whitening as a viable and accessible option for initial esthetic dentistry worldwide.

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Dr. Gerlach is Research Fellow in Worldwide Clinical Investigations, The Procter & Gamble Company, Mason, OH, USA. He and his colleagues at P&G hold national and international patents on products described in this special issue.

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Application of digital imaging in tooth whitening randomized controlled trials

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ABSTRACT: Purpose: The development of novel peroxide-based bleaching systems during the last several years has prompted the need for robust clinical methods to evaluate whitening response. Advances in digital camera technology and image analysis software provided the basis for an instrumental method to assess tooth color closely following a technique previously used to quantify plaque on tooth surfaces. *In vitro* and *in vivo* research was conducted to determine reproducibility of color measurements using this objective, digital imaging method. **Methods:** Each of the 16 tabs in a standard shade guide system was mounted in a jig, and measurement reproducibility was assessed *in vitro* from paired digital images collected over a 2-day period. Separately, clinical measurement reproducibility was assessed *in vivo* from paired images of 14 healthy adult volunteers collected over a 2-day period. From these digital images, mean L*, a*, and b* color values were derived for each of the 16 individual shade tabs (*in vitro* study), or the facial surfaces of the maxillary six anterior teeth (*in vivo* study) of the 14 subjects. For each data set, variability was determined using ANOVA, and between-visit color measurement reliability was determined from intra-class correlation coefficients (ICCs). **Results:** In the *in vitro* study, shade tab yellowness (b*) ranged from 9.0-18.6, lightness (L*) ranged from 63.4-76.2, and redness (a*) ranged from 0.9-3.6. Overall daily means differed by 0.08 units or less, and intra-class correlations for the image pairs were 0.998 for L*, 0.996 for a* and 0.998 for b*. In the *in vivo* assessment, the 14 volunteers exhibited considerable range in tooth color. Yellowness (b*) ranged from 13.5-21.3, lightness (L*) ranged from 69.2-78.0, and redness (a*) ranged from 5.2-8.8. Clinical measurement of mean tooth color from digital images was highly reproducible across visits. Intra-class correlations for the image pairs were 0.989 for b*, 0.970 for L* and 0.979 for a*. (*Am J Dent* 2007;20:7A-14A).

CLINICAL SIGNIFICANCE: Digital image analysis, which demonstrated high *in vitro* and *in vivo* color measurement reproducibility, may be broadly applied in whitening clinical trials or other applications requiring instrumental and objective assessment of tooth color.

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Introduction

Peroxide-based tooth whitening represents one of the most common esthetic procedures in dentistry. The considerable research spanning two decades and the recent extensive market experience with certain systems has resulted in intensive whitening being widely recognized by practitioners and patients as safe and effective.[1,2] Specific techniques differ with respect to peroxide source, delivery, regimen and other factors.[3] Despite these differences, the most popular techniques rely on well-recognized peroxide chemistry, where hydrogen peroxide is the oxidative species. Applied directly to tooth surfaces, peroxide diffuses to the chromophores within the structure of the tooth.[4] While the exact nature of the chromophores is unknown, many colored species contain carbon-carbon double bonds with which hydrogen peroxide can react to form an achromatic species.[5]

Peroxide concentration and contact time with tooth surfaces impact clinical response.[6,7] Use of a barrier like a strip or tray maintains a diffusion gradient with each treatment.[8] The technique is typically repeated over days, weeks or even months, depending on the nature of the discoloration.[9] Increasingly, behavioral factors are recognized to contribute to compliance, and ultimately, clinical response. Recent research has focused on identifying more acceptable whitening, through treatments focused on convenience, cost, and other factors. Advent of the easy-to-use whitening strips represents, perhaps, the most prominent example.[10] Hydrogen peroxide concentrations of up to 14% have been used with low unit-dose strips to yield appreciable whitening without meaningful side effects.[11]

Clinical response following repeated topical peroxide application to teeth is commonly referred to as "whitening". While the terminology may overlap with abrasive or chemical removal of superficial tooth stains (sometimes referred to as extrinsic stain), there is a specific physical chemistry with the peroxide-based whitening "intensives" (repeated use, longer contact time), and a unique, perceptible clinical response.[12] Perceived tooth color following treatment, like other visualization, is the function of spectral reflectance, incident light and its psychophysical interpretation.[13] Various methods have been used to quantify tooth color in various color spaces. The most prominent of these is the international standard CIELAB color space. Using this color space, colors can be described in the three dimensional coordinate space as L* (white-black), a* (red-green) and b* (yellow-blue).[14] For dentistry, differences in tooth color can be quantified in both preclinical and clinical settings as CIELAB units. These outcome values can be directly correlated to color perception, preference and meaningfulness.[15,16] Use of peroxide-based whitening intensives leads to measurable differences in all three CIELAB parameters, specifically increased lightness (+ΔL*), decreased redness (-Δa*) and decreased yellowness (-Δb*). Where there is sufficient improvement (-Δb* and +ΔL*), individuals characterize the color change as "whitening", and discriminate levels of improve-

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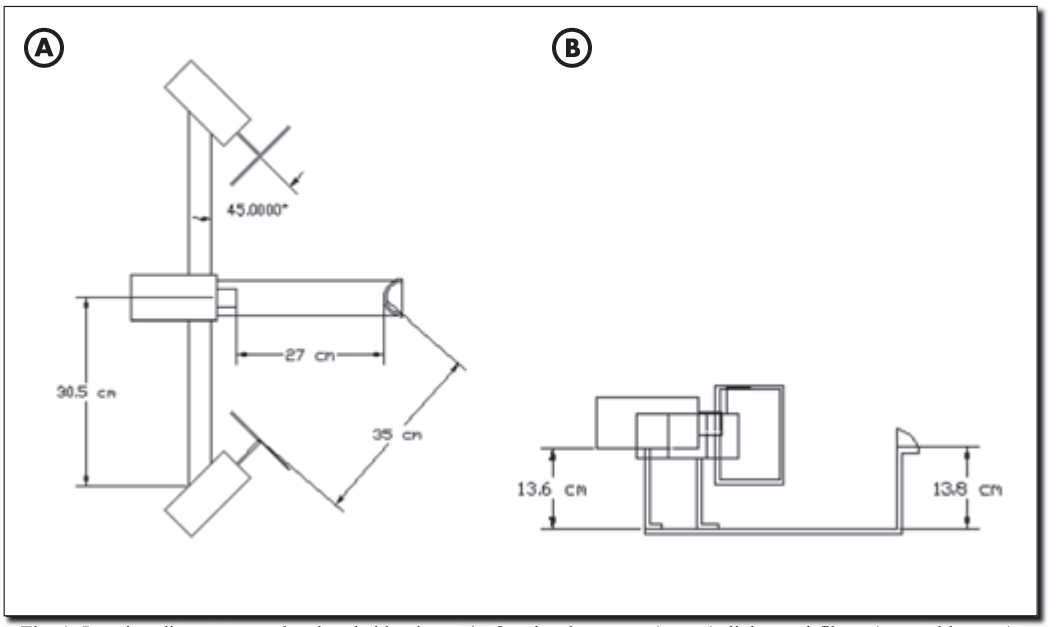

Fig. 1. Imaging diagrams, overhead and side views. **A.** Overhead: camera (center), lights and filters (top and bottom), and chinrest (right); **B.** Side: camera (left), lights and filters (left center), and chinrest (right).

ment or acceptability.[16]

There have been a number of human studies that have evaluated clinical whitening relative to baseline or experimental controls. In the initial whitening research, outcomes were measured as shade change, quantified using a variety of shade guides.[17-19] Limitations with shade guide usage are legendary in clinical dentistry, since teeth are inconveniently not a single shade, and various physical, environmental and behavioral factors contribute to difficulties in shade assessment.[20,21] While some factors (such as wall color or installed lighting) may be described, no published shade guide trial to date has disclosed use of sufficient controls recommended for matching a single dental restoration.[20] Analysis may be even more problematic than assessment, as most whitening studies reduce complex multi-dimensional color differences to a single, linear variable, usually through an ordering of shade tabs.

Early on, researchers recognized limitations in subjective assessment of whitening, and the need for sensitive measurement methods to assess or compare whitening products.[22,23] Several used colorimeters, spectrophotometers, or other instruments to objectively measure clinical response following whitening.[24-27] Published usage of these instrumental methods was limited to a single study, or sometimes, a few repeated trials at a single site. Prominent techniques used individual custom stents, mouthguards or other devices for positioning. While contributing to clinical trials complexity, these approaches generally were confined to a few site measurements only a few millimeters in diameter.[22,23] The relevance of these spot measurements to overall appearance was unproven. As such, prior to 2000, there was little-to-no systematic use of objective instrumental methods in whitening clinical trials, and inference from the few reported methods to broad populations was largely unknown.

Around that time, our group began a series of randomized controlled trials to assess clinical response following use of various whitening systems, research that ultimately led to the introduction of the whitening strips.[28] We sought a clinical whitening method that was valid, unbiased, relevant, acceptable, efficient and archival in nature. Given the ambitious nature of the planned clinical research, we desired a robust method that could be reapplied multicenter, broadly across populations and geographies, rather than confined to a single investigator or site. The considerable development in digital camera technology and image analysis software provided the basis for a new instrumental method. Our approach followed a technique used to quantify plaque on tooth surfaces.[29] The method, where digital images were used to quantify fluorescein-disclosed plaque on tooth surfaces, exhibited considerable measurement sensitivity for use in various plaque-related clinical trials. For whitening, new *in vitro* and *in vivo* research was conducted to establish reproducibility and reliability of the objective, instrumental method to measure tooth color.

Materials and Methods

Digital imaging system - A standard, fixed set physical set-up was used to ensure reproducible image capture conditions with respect to light—subject—camera geometry (Fig. 1A). A digital camera (HC Series 3CCD[a]) was mounted a fixed distance away from a cup-type chin rest with lights positioned on each side of the camera. The distance from the body of the camera (front) to the front of the chin rest was 27 cm. Dedo lights[b] were mounted on each side of the camera and equipped with a series of filters. Each light was positioned 30.5 cm from the system centerline to the bulb in forward most position. The lights were placed at an angle of 45 degrees relative to the centerline of the system. The light filters were a 13.97 x 12.1 (w x h) cm series construction of a therma shield, a bluing filter and a linear polarizer. The heat shield served as a comfort measure for the subjects, the polarizer provided polarized light to the tooth surfaces and the bluing filter brought color temperature into the 5000K range. The filters were attached to the front of the lights using the standard Dedo mounting bracket which positions the filters 6 cm from the front of the light lens. Each Dedo light was fitted with a xenophot 150W,

24V bulb powered with a tunable voltage power supply and powered in series for a nominal total light bulb voltage 48V. A power supply equipped with a variable rheostat was used to set the voltage to approximately 46V. The -2V difference between the nominal voltage of the light series and the set-point protected against accidental overpowering of bulbs and provided adjustment latitude during calibration and standardization. The room conditions were selected to eliminate any extraneous light from windows or other light sources. The only light in the room was provided by the imaging system light sources. The system was placed approximately 2 m from camera-visible walls, such that the camera was not able to detect light reflected off of the walls from the Dedo lights.

A Fujinon 4 x 75 zoom lens was attached to the camera. The focal plane of the lens was set at 16 mm from the lens. The lens was locked down to prevent adjustments. A polarizer was added to the zoom lens and rotated to a position of cross polarization relative to the polarizers on the lights. This cross polarization was set by placing a ¾" chrome ball at the focal plane and rotating the polarizer on the lens until the glare spots were minimized. This combination of lighting, camera and lens settings produced RGB values of approximately (250, 250, 250) for a pure white sample.

The height of the chin rest was mounted such that the floor of the chin rest was 13.8 cm from support surface (Fig. 1B). Similarly, the bottom of the camera base was 13.6 cm from the support surface. The Fuji series camera was controlled by a PRISM PRI SM-N7-ATX portable 40 GB Win 98. Calibration and image capture were accomplished with custom visual basic programs as the interface between the operator and Optimas (Optimas 6.5[c]), image analysis software.

At the start of each image capture session and hourly thereafter, the system was black/white balanced and then standardized to two color reference standards. The black balance was established by putting the lens cover on and capturing an image. The black balance was adjusted until uniformity was achieved across the red, green and blue channel. Next, a 7.6 cm x 7.6 cm 70% gray MacBeth standard (N-8, Munsell[d]) was placed at the focal plane. The reference standard image was captured and the white balance was adjusted to bring the color channel values to uniformity across red, green and blue (RGB) channels at approximately 200. After white balancing, a second image of the gray standard was captured to check for abnormalities in the gray standard. The gray value of each pixel was normalized to the mean intensity of the image to generate a position dependent ratio correction for any variations in lighting intensity across the field of view of the camera. This intensity correction was applied to each subsequently captured image. Next, an image of a 22 chip color standard was captured. The average red, green and blue values of each color chip were extracted using Optimas.[c] The color values were compared to a standard set of values which served as the standardization point for the camera. These standardization values were determined by using several cameras to capture images under the conditions set forth above. If the red, green and blue values were within pre-established tolerance of 5 RGB values, then no further system adjustment was needed. If the values were outside of the established tolerances, the system was adjusted, typically with light intensity, to get within precalibration tolerances. To color correct for remaining differences between the captured values and the standard values, a 3rd order polynomial color correction was established by regressing the captured values for each channel against the standard values including the cross channel terms where:

$$R_{corrected} = f(R_{input}, G_{input}, B_{input})$$
$$G_{corrected} = f(R_{input}, G_{input}, B_{input})$$
$$B_{corrected} = f(R_{input}, G_{input}, B_{input})$$

After successful standardization, the position dependent intensity correction and the color correction were applied to each subsequently captured image until the next calibration cycle. Each calibration set including raw values and calibration results were written to a text file each time the system was calibrated.

In vitro reproducibility - *In vitro* reproducibility was assessed by measuring the color of each tab of a Vita Pan Classic[e] shade guide system. Digital images of each tab were collected on 2 consecutive days using the same shade guide. Each day, the system was turned on and calibrated according to the standard operating procedure. After warm up and calibration, each chip was individually measured in random order. For imaging, each shade tab was inserted in a jig and oriented at similar height and distance from the camera and lights as typical of actual clinical measurement. Upon completion, the system was shut down until the next test day. After all images were captured, the L*, a* and b* color values of each tab were extracted using the standard image analysis procedure. The single set of color values for each tab represents the average color over the entire tab with each pixel of the tab image being assigned equal weight.

In vivo reproducibility - *In vivo* reproducibility was assessed from digital images of the anterior facial dentition of 14 healthy adult volunteers. Digital images of each subject were collected on 2 consecutive days using a standard method. Each day, the system was turned on and calibrated according to the standard operating procedure. After warm up and calibration, individual subjects used cheek retractors to pull the cheeks back and allow for unobstructed illumination of the tooth surfaces. Prior to use, the clear retractors were given a matte finish to avoid the possibility of producing glare in the image. Each subject then put his or her chin in the rest, while the operator provided instructions based on a live output view from the camera to properly align the subject. Subjects were instructed to position the maxillary and mandibular incisors to avoid overlap of the maxillary and mandibular teeth, to look straight on to the camera to avoid any left-right rotation and forward or backward tilting of the head, to pull retractors by the ends of the handles toward the ears to avoid any shadowing resulting from the retractors or the subjects hands, and to retract the tongue away from the teeth. If excess saliva was observed, the subject was instructed to remove the retractors, and close his or her mouth to clear the saliva, for repositioning. When in position, the image was captured, processed through the intensity and color correction, and saved according to subject number and visit sequence. Upon completion, the system was shut down until the next test day. After all images were captured, the L*, a* and b* color values of the facial surfaces of the maxillary anterior teeth were extracted using the standard image analysis proce-

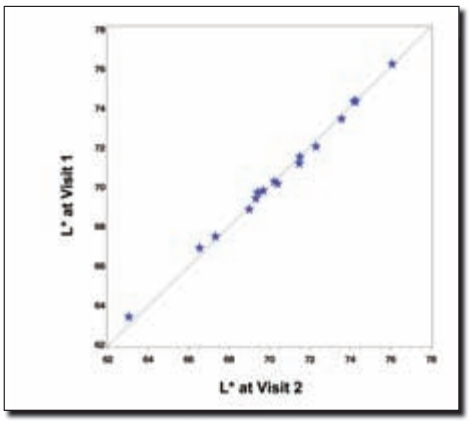

Fig. 2. *In vitro* reproducibility of Mean Shade Tab Lightness (L*).

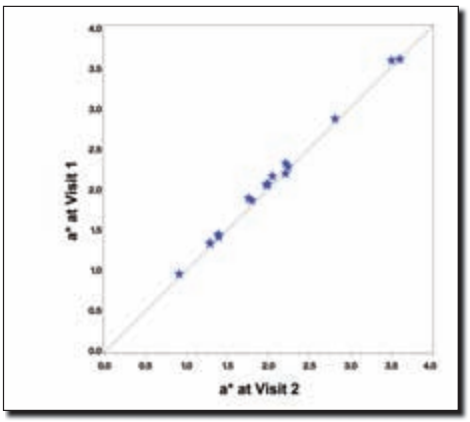

Fig. 3. *In vitro* reproducibility of Mean Shade Tab Redness (a*).

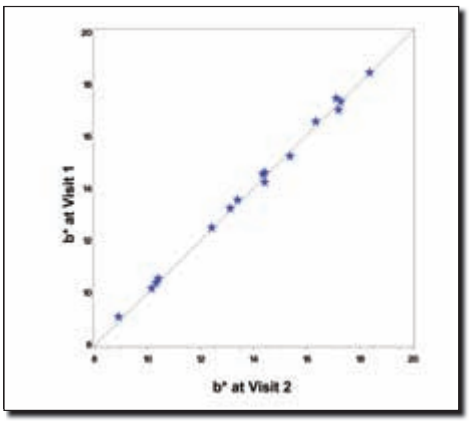

Fig. 4. *In vitro* reproducibility of Mean Shade Tab Yellowness (b*).

dure. The single set of color values for each subject represented the average color over the arch with each pixel of the tab image being assigned equal weight.

Image analysis - The pixels of each captured image were classified into categories using the previously published discriminant analysis.[29] This method allowed the teeth to be objectively identified in the image. The discriminant analysis was established by sampling approximately 2000 pixels of teeth, stain, dark areas between teeth and oral soft tissue from representative images captured under the standardization process. The pooled RGB values of the captured pixels from each class were captured and color channel means, within color channel variance and cross color channel co-variances were calculated for each class which was sampled. The resultant discriminant model then assigned each pixel to the nearest class based on the distance of the color of each pixel to each predefined class using the following generalized squared distance from pixel **x** to class t:

$$D_t^2(\mathbf{x}) = (\mathbf{x}-\mathbf{m_t})' * \mathbf{S_t}^{-1} * (\mathbf{x}-\mathbf{m_t}) + \log |\mathbf{S_t}|$$

where **x** is a 1x3 matrix of the red, green and blue values of the pixel to be classified and $\mathbf{m_t}$ is a 1x3 matrix containing the average red, green and blue values of class t.

The covariance matrix $\mathbf{S_t}$ for class t was:

$$\mathbf{S_t} = \begin{array}{c|ccc} & \mathbf{R} & \mathbf{G} & \mathbf{B} \\ \mathbf{R} & \text{Cov (R,R)} & \text{Cov (R,G)} & \text{Cov (R,B)} \\ \mathbf{G} & \text{Cov (R,G)} & \text{Cov (G,G)} & \text{Cov (B,G)} \\ \mathbf{B} & \text{Cov (R,B)} & \text{Cov (B,G)} & \text{Cov (B,B)} \end{array}$$

$$\text{Cov}(X,Y) = 1/n * \Sigma (X_i - u_X)(Y_i - u_y)$$

where:

X_i and Y_i represent the i-th red, green or blue value in class t

u_x and u_y are the mean red, green or blue value of class t.

The inverse matrix ($\mathbf{S_t}^{-1}$) was defined such that $\mathbf{S_t}^{-1} * \mathbf{S_t}$ is the identity matrix:

	R	**G**	**B**
R	1	0	0
G	0	1	0
B	0	0	1

After classification, the pixels of each class were then counted and averaged together to produce average RGB values for each class. The RGB values were then converted to CIE L*a*b* values. The conversion to L*a* b* was accomplished using a regression of the RGB color values of the color standard against the standard assigned MacBeth L*a*b* values under illuminant C conditions. The regression produced the following RGB to L*a*b* calibration equations. Because each camera is standardized to a reference set of RGB values, a single RGB to L*a*b* conversion can be used across all cameras.

$L^* = 0.104*R + 0.183*G + 0.00847*B + 20.12$ (R^2=0.996)
$a^* = 0.319*R - 0.468*G + 0.138*B + 3.82$ (R^2=0.952)
$b^* = 0.176*R + 0.262*G - 0.425*B - 1.78$ (R^2=0.996)

Clinical measurement reproducibility was assessed from the paired shade guide images of 16 shade tabs collected over 2 days (*in vitro* study), and paired images of 14 healthy adult volunteers collected over 2 days (*in vivo* study). Collected digital images were analyzed using the standard approach, and mean L*a*b* values were derived for each shade tab and for facial surfaces of the maxillary six anterior teeth of each study subject. Variability was determined using ANOVA. Between-visit color measurement reliability was assessed from intra-class correlation coefficients (ICCs). With continuous measures like CIELAB, ICC measures both the correlation and scale agreement. An ICC was calculated separately for b*, L* and a* as:

$$\text{ICC} = \sigma_\beta^2/(\sigma_\beta^2 + \sigma_W^2 + \sigma_\varepsilon^2)$$

where σ_β^2 was between subject variability, σ_W^2 was within-subject variability, and σ_ε^2 was error variance. Using this method, each ICC could range from 0-1, where 0 represented only a chance relationship between the first and second image, while 1 represented perfect agreement between pairs.

Results

In vitro reproducibility - When measured at the bench, digital image analysis showed the 16 shade tabs to exhibit considerable range in b* and L* color. Yellowness (b*) ranged from 9.0–18.6, lightness (L*) ranged from 63.4–76.2, and redness (a*) ranged from 0.9–3.6. Comparing days, the overall tab means (SD) were 70.59 (3.19) for L*, 2.09 (0.76) for a*, and 14.07 (2.93) for b* on initial measurement, and 70.54

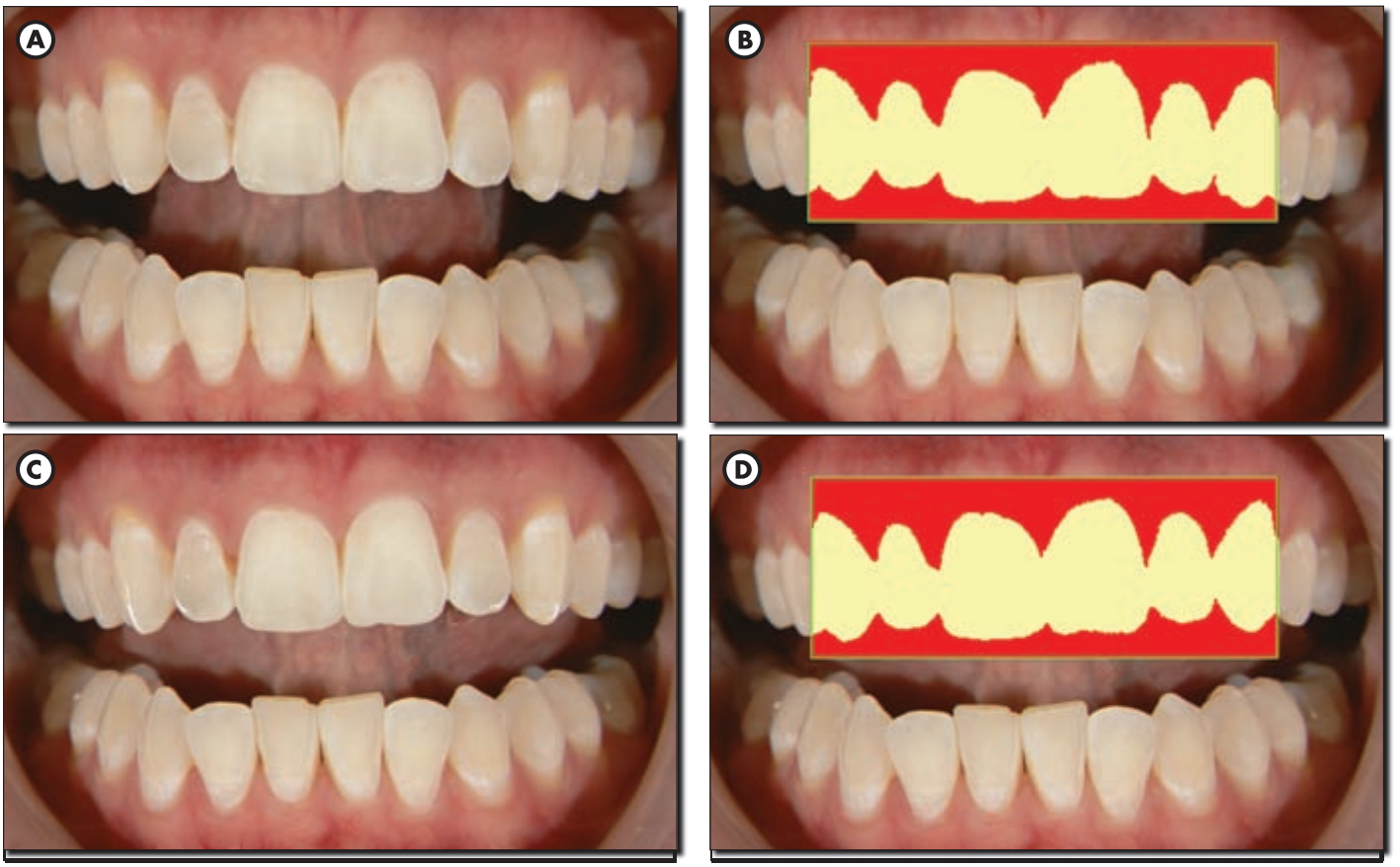

Fig. 5. Paired images and examples of image analysis of six maxillary anterior teeth (Subject 5429). **A.** Image #1; **B.** Example image analysis #1; **C.** Image #2; **D.** Example image analysis #2.

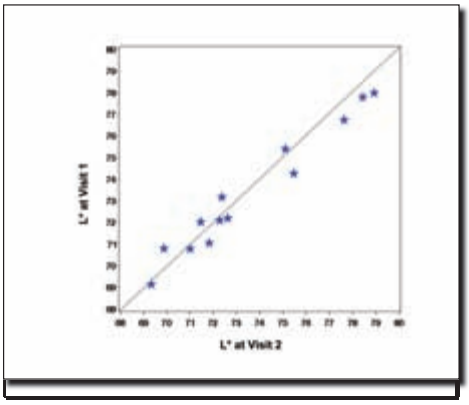

Fig. 6. *In vivo* reproducibility of mean tooth lightness (L*) by visit.

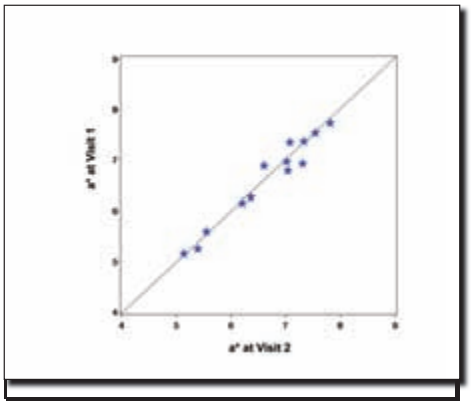

Fig. 7. *In vivo* reproducibility of mean tooth redness (a*) by visit.

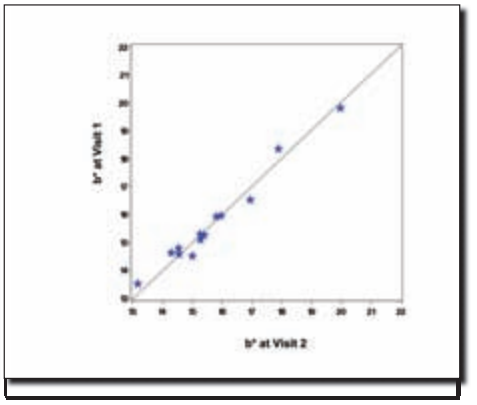

Fig. 8. *In vivo* reproducibility of mean tooth yellowness (b*) by visit.

(3.27), 2.03 (0.76) and 13.99 (2.92) with next day replication. Overall daily means differed by 0.08 units or less. Each of the paired measurements was highly reproducible (Figs. 2-4). This was evident across the range of tabs and colors in the 16-tab sample. The *in vitro* ICCs for the daily image pairs were 0.998 for L*, 0.996 for a* and 0.998 for b*.

In vivo reproducibility – Figure 5A-D displays the captured images and examples of image analysis of six maxillary anterior teeth for one subject. Mean CIELAB tooth color was derived for the maxillary anterior six teeth, relative to calibration standards.

Overall, the 14 volunteers exhibited considerable variability in the color of the facial surfaces of the six maxillary anterior teeth. Individual subject means ranged from 13.5–21.3 for yellowness (b*), 69.2–78.0 for lightness (L*) 5.2–8.8 for redness (a*). Each of the paired measurements was highly reproducible (Figs. 6-8). This was evident across the range of teeth, pixel classifications, and colors in the 14-subject sample. The *in vivo* ICCs for the daily image pairs were 0.989 for b*, 0.970 for L* and 0.979 for a*.

Discussion

There has been considerable attention to clinical research on peroxide-based tooth whitening, since the introduction of the first marketed systems in the late 1980s. Clinical response has been reported in various case studies, and uncontrolled or controlled clinical trials. There has been little systematic eval-

uation of the effectiveness of peroxide-based tooth whitening systems, with evidence-based reviews sometimes confined to a handful of studies using subjective assessments of restricted populations from research conducted at only a few sites.[30] To address research needs in a rapidly changing environment, we sought an objective clinical method that was sufficiently valid and robust for use as part of a diverse and comprehensive clinical testing program.[10] The technique, an adaptation of a dental plaque method, used digital image analysis to quantify tooth color *in vivo* under controlled lighting conditions.[29] The clinical reproducibility of the digital imaging method was tested using paired images from 14 adults. This reproducibility model assumed tooth color to be relatively constant over the course of 2 days. Within-subject measurement variability was introduced *via* differences (if any) in imaging system calibration, subject positioning, camera focus, lighting and other factors, consistent with longitudinal clinical trials research. In the study, clinical measurement of mean tooth color from digital images was highly reproducible across visits. Intra-class correlations between image pairs exceeded 0.97 for the b*, L* and a* color parameters.

While the clinical reproducibility was high (ICCs greater than 0.97), bench reproducibility was even higher. Paired measurements of shade tabs one day apart yielded ICCs ranging from 0.996-0.998 for each of the individual color parameters. This was anticipated, as measurement should be more reproducible on the bench compared to in the mouth. Although tooth color is often thought of as constant, daily variation in diet or oral hygiene, lip and head positioning, tooth shape (rather than tab shape), and other nuances may contribute to subtle differences in measured color. Nonetheless, the shade tab measurements were germane to clinical trials. The tabs were generally tooth-shaped (or more specifically, central incisor-shaped). The range of tooth colors in the shade tabs generally overlapped those seen in the *in vivo* testing. This was particularly evident for b* and L*, the primary perceptual response variables with tooth whitening, but less so for a*.[16] Of these, the red-green (a*) minor component in whitening, may be subtly impacted by color reflection from the typically reddish and adjacent oral soft tissue or alternatively the shade guides may not be reflective of "redness" of *in vivo*, vital teeth. (There was no comparable adjacent reddish border in the *in vitro* study.) Nonetheless, the generally comparable shapes and color ranges of the tabs suggest relevance of the *in vitro* measurements to broader clinical applications. Overall, these bench measurements likely serve as an upper limit on daily method reproducibility for tooth color when subject-related variability is eliminated.

Since 2000, there has been an extensive and accumulating body of evidence on the use of this digital image analysis method in randomized controlled whitening studies. A comprehensive bibliography may be found at www.dentalcare.com. These have included notable, double-blind, placebo-controlled trials of various peroxide-based whitening intensives.[31-34] Another series of clinical studies compared strips, trays or other systems head-to-head.[11,16,35-44] Study populations have typically been general, and not confined to "A3" or some other optimally responsive group. Use of digital imaging in studies involving children and adolescents further suggests broad potential application of the method in clinical research.[45-47] The digital imaging analysis endpoints, especially change in yellowness (Δb^*) and lightness (ΔL^*) have been previously shown to be relevant to self-perception of tooth color.[16] Importantly, outcomes from this complex clinical research program are plausible. In head-to-head testing, use of barriers (like a strip or tray) to maintain a peroxide diffusion gradient resulted in significant increased whitening ($-\Delta b^*$ and $+\Delta L^*$) compared to peroxide delivery without a barrier.[48-50] Few clinical studies other than those using digital imaging have demonstrated this simple result.

Ranging studies, best exemplified by the classic dose response trial, represent perhaps the greatest methodological challenge in clinical research. These double-blind studies, usually involving at least three treatment groups (or doses), may best illustrate the measurement sensitivity of any clinical method. For peroxide, the dose response chemistry is quite clear, in that tooth whitening is both peroxide concentration and contact time dependent.[6] Despite the availability of various concentrations of peroxide gels in trays, strips and other systems, there are very few examples of successful, adequate and well-controlled ranging studies in the whitening clinical trials literature.[51] Importantly, the digital imaging method has shown dose response measurement sensitivity for various peroxide concentrations, under different delivery conditions, in double-blind clinical trials conducted at sites within and outside the US.[7,35] These three-group trials have shown the impact of both peroxide concentration and time on clinical whitening, as measured using CIELAB. We are unaware of other instrumental or clinical methods having a similarly robust demonstration of dose ranging sensitivity. Pending such evidence, digital imaging analysis likely represents the optimal method for dose ranging, comparative trials of peroxide-based systems or post-treatment color monitoring (color stability), since these study designs may likely necessitate sufficient measurement sensitivity to adequately discriminate treatment effects.

In addition to the measurement sensitivity, instrumental methods may help limit introduction of bias in clinical trials research. Irrespective of causality, such systematic error can contribute to anachronistic or confounded outcomes. With digital image analysis, the images are collected and analyzed in a standard fashion, without respect to treatment assignment, or any other aspects of study design. Digital images are collected without regard to temporality (pre-treatment, baseline, end-of-treatment, or post-treatment), adverse events (presence or absence of differential diagnostic tooth sensitivity), design anomalies (such as pre-fabricated trays, instructed usage or others), usage (such as compliance or taste), and other factors that may contribute bias to subjective examination. Use of an unbiased method is of obvious merit in comparative clinical trials involving distinct systems, where differences in delivery or regimen may impact blinding of the research team. It also may be important in placebo-controlled whitening trials, where the maxillary arch may be treated first. This contrast between arches has long been recognized as a patient motivation or compliance monitoring "tool".[52] Unfortunately, the visible presence of whitening (such as maxillary *versus* mandibular) could introduce bias into clinical grading, since treatment assignment may be discerned, especially in placebo-controlled trials.

Digital imaging analysis of tooth color also has other characteristics that may contribute to data integrity. The archival image serves as evidence of the clinical case presentation at the time of image capture. This clinical presentation may be used in planning secondary analyses, or for follow-up in data quality assessment. With digital imaging, date, time, chain of custody and other factors are captured along with the color variables, consistent with US Food and Drug Administration guidelines for electronic data capture and analysis. While always providing evidence, the digital images may become actual evidence. Such was the case in 2004, when advertising claims based on digital imaging were sustained in a lawsuit in US Federal Court.[53] Peer review during litigation involves a much higher level of scrutiny (time, experts, documents and the like) compared to scientific publication, or even voluntary arbitration. We are unaware of any other whitening method that has successfully undergone a similar degree of evaluation in the literature and the courts.

Additional research would be needed to compare digital image analysis to other whitening methods. While instrumental methods offer significant advantages, each instrumental system may provide somewhat different data based on input differences such as lighting and other conditions, used with that specific approach. Clinical studies that directly compare instrumental methods would aid in interpretation. Comparisons between digital imaging analysis and shade guides are more complex. Unlike digital image analysis, shade differences are not linear, and some numerical shade reductions may not even be indicative of whitening. Nonetheless, each individual step change (A1-to-B1 and C4-to-A4) represents a different set of changes in CIELAB color space. Standard shades can be reproducibly measured, and between-tab differences quantified using digital imaging methods. Raw tooth-specific shade data (before and after), and not just group means, would be needed in order to approximate the color change seen in shade guide studies.

Prior to the digital image analysis method, the majority of clinical research on tooth whitening was limited to U.S. studies conducted at relatively few sites. Application of digital image analysis may have particular application in expanding whitening clinical trials research broadly to other locations, including studies outside the U.S. The entire system (camera, lighting, computers and related materials) for image capture fits on a small table top. It can be easily crated and shipped *via* commercial carrier to clinical sites throughout the world, and then set up and calibrated within a few hours. The only site requirements are a reliable power source, and a relatively dark room. The technique does not require specially painted walls, fixed lighting, or other such infrastructure standards, such as those advocated for simple shade collection.[20] Each image can be collected in about 1 minute, by a local operator, using only the local language for subject interaction. Digital data may be stored and analyzed locally, and/or transmitted electronically for evaluation. As such, this objective method may be optimal for use in multicenter or multinational whitening clinical research programs.

Clinical trials play a prominent role in safety and effectiveness testing, with the highest evidence provided from integrated analyses across studies, sites and populations. Digital image analysis, an objective and robust method for quantifying tooth color, was introduced to facilitate a comprehensive and diverse clinical research program on peroxide-based whitening. This method exhibited a high level of *in vitro* and *in vivo* measurement reproducibility, as evidenced by intra-class correlation coefficients for b*, L* and a* tooth color exceeding 0.97.

a. Fuji Film Corp, Tokyo, Japan.
b. Dedotec USA, Ashley Falls, MA, USA.
c. Media Cybernetics, Inc., Silver Spring, MD, USA.
d. GretagMacbeth, New Windsor, NY, USA.
e. VITA Zahnfabrik, Bad Säckingen, Germany.

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Professional whitening strips in a university population

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ABSTRACT: Purpose: To evaluate the clinical response of a professional whitening strip system used by a university-based population residing in Mexico City, Mexico. **Methods**: A randomized, double-blind, placebo-controlled study was conducted to evaluate the safety and efficacy of 6.5% hydrogen peroxide whitening strips used over a 3-week period. A total of 30 volunteer students and staff at the National Autonomous University of México (Mexico City) were randomly assigned to the peroxide or placebo strip groups. Strips were worn for 30 minutes two times a day for 3 weeks. Efficacy was evaluated using digital image analysis to assess change in L* a* b* tooth color, while safety was assessed by oral examination and subject interview. **Results**: Relative to placebo, the 6.5% hydrogen peroxide strip group experienced nearly a 4-unit color improvement (Δb*). Treatment groups differed significantly (P< 0.0001) with respect to yellowness (Δb*), lightness (ΔL*) and redness (Δa*). Adjusted mean (SE) overall color improvement (ΔW*) was -4.76 (0.27) for the peroxide strips, compared to the near zero, -0.21 (0.28) for the placebo control. Strip use was well tolerated. Minor, transient tooth sensitivity occurred more frequently in the peroxide group, and overall, no subjects modified or discontinued treatment early because of adverse events. (*Am J Dent* 2007;20:15A-18A).

CLINICAL SIGNIFICANCE: This double-blind clinical trial in a university population demonstrated highly significant and appreciable L*a*b* color improvement for the professional 6.5% hydrogen peroxide whitening strips after 3 weeks use.

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Introduction

Professional tooth whitening with peroxide represents one of the most common esthetic procedures in dentistry today. The technique has been widely available since the introduction of the so-called "nightguard" trays in the late 1980s.[1] Hydrogen peroxide or carbamide peroxide are both used, sometimes in combination, to effect tooth whitening. Safety data is extensive, with up to 12 years post-treatment monitoring without meaningful findings other than tooth whitening.[2] Treatment may be accomplished at-home using one of the custom tray systems,[3] *via* in-office application,[4] or through some combination where treatment is first initiated in-office, and then continued at-home.[5,6] Peroxide concentrations range from 3-30+%, depending on the peroxide source and method of delivery.[7] Selection may be based on patient preference through oral status, compliance and other factors.[8]

A "trayless" option for professional at-home treatment (Crest Whitestrips Professional[a]) was introduced in 2002.[9] With this system, a 6.5% H_2O_2 gel is applied to the facial surfaces of the anterior dentition over a 21-day period using a flexible strip.[10] Such delivery has been reported to offer certain advantages *vs*. custom tray-based systems relative to peroxide dose, contact time, and ease of use.[11] Because the strip can be adapted directly to the user's teeth, steps for tray fabrication, adjustment and delivery can be eliminated. Treatment can be initiated at the time of diagnosis using the uniform and pre-dispensed individual strips. In addition, individual strips are easily portable, and disposable, the latter of which limits need for tray cleaning, storage, or maintenance. Clinical response is reported to be better than that seen with daytime use of popular trays.[12,13] Evidence of safe and effective use has also been established in clinical and preclinical studies comparing whitening strips to various negative and positive controls.[14,15]

Previous research on 6.5% hydrogen peroxide strips had evaluated color change in adults[16] and adolescents.[17,18] The clinical research was primarily conducted in the U.S. on a general population. This clinical research was planned for Mexico City to evaluate the robustness of the method and clinical response relative to studies reported in the U.S. This new study specifically targeted a university-aged population (20-30 years old), because previous research has demonstrated this age group to be aware of tooth discoloration, and interested in esthetic dentistry.[19]

Material and Methods

This was a prospective, randomized, double-blind, placebo-controlled single-center study conducted at the National Autonomous University of México, Mexico City, Mexico. The research protocol and informed consent were reviewed and approved by an institutional review board prior to study initiation. The study population was recruited from the university environment, and included healthy adult students and staff 18-30 years of age. After informed consent, 30 subjects were randomly assigned to either a 6.5% H_2O_2 strip (Crest Whitestrips Professional[a]) or placebo strips. Treatment groups were balanced for baseline age and color. For blinding purposes, each subject was provided an identically-appearing kit box labeled only with a unique subject number, and pertinent cautionary/use statements required for investigational research. Each kit contained 42 maxillary strips (sufficient for 21 days usage) in individual foil pouches. Subjects were also provided a marketed anticavity toothpaste, extra-soft toothbrush and written instructions for use. Strip usage was twice daily for 30 minutes over a 21-day period, at-home and unsupervised.

Efficacy was assessed as change in tooth color as measured from standard digital images of the maxillary anterior teeth. This objective and instrumental color measurement method had previously been used to demonstrate a peroxide concentration response for tray and strip whitening systems.[14]

Table 1. Baseline demographic characteristics and color parameters.

Baseline statistic	Peroxide strip (n = 15)	Placebo strip (n = 15)	Overall (n = 30)	Two-sided P-value
Age (Years)				
Mean (SD)	23.0 (1.89)	23.7 (3.06)	23.4 (2.53)	0.4361
Minimum-maximum	20.0 - 26.0	20.0 - 30.0	20.0 - 30.0	
Gender				
Female	12 (80.0%)	13 (86.7%)	25 (83.3%)	1.0000
Male	3 (20.0%)	2 (13.3%)	5 (16.7%)	
Tobacco use (Daily)				
No	8 (53.3%)	4 (26.7%)	12 (40.0%)	0.2635
Yes	7 (46.7%)	11 (73.3%)	18 (60.0%)	
L* (Lightness)				
Mean (SD)	75.6 (1.64)	75.8 (1.40)	75.7 (1.53)	0.6969
Minimum-maximum	72.9 - 78.0	72.5 - 77.6	72.5 - 78.0	
a* (Red-green)				
Mean (SD)	6.1 (0.59)	5.9 (0.50)	6.0 (0.55)	0.3733
Minimum-maximum	5.3 - 7.8	5.1 - 6.8	5.1 - 7.8	
b* (Yellow-blue)				
Mean (SD)	19.7 (1.07)	19.8 (0.96)	19.8 (1.02)	0.9153
Minimum-maximum	18.5 - 22.8	18.5 - 21.9	18.5 - 22.8	
W* (Composite color)				
Mean (SD)	32.0 (1.69)	31.8 (1.36)	31.9 (1.51)	0.7537
Minimum-maximum	29.5 - 35.2	29.9 - 34.3	29.5 - 35.2	

Using this method, subjects were first positioned in a chin rest, retractors were inserted, and standard bilateral illumination of the arch was obtained from two 150-watt lights and linear polarizers. Images were then captured using a photographic system using a HC Series 3CCD high resolution digital camera[b] and a Fujinon A8x12BMD, 1:2.8/12-96 mm zoom lens,[b] and a personal computer. Color measurements were calibrated to known standards daily prior to use and hourly thereafter to assure proper operation. Safety was assessed by clinical examination and interview to ascertain any tooth sensitivity or oral irritation that may have occurred during treatment.

Baseline and end-of-treatment digital images were analyzed using a standard method in order to derive red-green-blue values for the six maxillary teeth. These average values were transformed to yield CIELAB tooth color values for b* (yellow – blue), L* (lightness), and a* (red – green).[20] Color change was calculated for each subject by comparing mean color at end-of-treatment to baseline, where $\Delta b^* = b^*_{visit} - b^*_{baseline}$, $\Delta L^* = L^*_{visit} - L^*_{baseline}$, $\Delta a^* = a^*_{visit} - a^*_{baseline}$. Reduction in yellowness (Δb*) was selected *a priori* as the primary endpoint, because this parameter has been shown to correlate with subjective perception of whitening following vital bleaching.[21] In addition, a composite directional color parameter (ΔW*) was calculated to measure overall color change relative to an abstract white color, represented in L* a* b* space as L* = 100, a* = 0, b* = 0. Using this method, W* represented the vector distance between individual L* a* b* color coordinates and white, derived from: $W^* = (a^{*2} + b^{*2} + (L^*-100)^2)^{1/2}$. Change in the closeness to white (ΔW*) with treatment was calculated as: $\Delta W^* = W^*_{visit} - W^*_{baseline}$, where negative ΔW* indicated color coordinates that were closer to white.[16] Between-group comparisons of color change used ANCOVA, with baseline color as the covariate. All comparisons were tested at the two-sided 0.05 level of significance. Subject interview and oral examination results were summarized overall and by group.

Results

Thirty subjects were randomized, 15 to each group. The study population was predominantly female (83%) with an age range of 20-30 years. Eighteen (60%) of the subjects routinely used tobacco products (Table 1). The population exhibited appreciable discoloration at baseline, with overall means (SD) of 19.8 (1.02) for b*, 75.7 (1.53) for L*, and 6.0 (0.55) for a*. Groups were balanced with respect to demographic characteristics, and behavioral parameters, as well as L*a*b* color parameters. All 30 subjects completed the study. Prior to unblinding the study, one subject had a protocol deviation and was not included in the efficacy analysis. After database lock, that individual was found to have been assigned to the placebo strip group. The remaining 29 subjects were included in the efficacy analysis.

Table 2. Treatment comparisons at Day 21; ANCOVA: adjusting for baseline color (N = 29).

Color / Treatment	Baseline mean (SE)	Adjusted mean change from baseline (SE)	Treatment comparison	
			Treatment difference (SE)	Two-sided P-values
Δb*(Yellow-blue)				
Peroxide strip	19.73 (0.28)	-4.59 (0.23)	-3.93 (0.33)	< 0.0001
Placebo strip	19.69 (0.25)	-0.66 (0.23)		
ΔL*(Lightness)				
Peroxide strip	75.61 (0.42)	2.33 (0.23)	2.61 (0.33)	< 0.0001
Placebo strip	75.92 (0.38)	-0.28 (0.24)		
Δa*(Red-green)				
Peroxide strip	6.08 (0.15)	-1.20 (0.09)	-1.10 (0.13)	< 0.0001
Placebo strip	5.85 (0.13)	-0.10 (0.09)		
ΔW*(Composite color)				
Peroxide strip	31.98 (0.44)	-4.76 (0.27)	-4.55 (0.40)	< 0.0001
Placebo strip	31.67 (0.35)	-0.21 (0.28)		

After 21 days of product use, the 6.5% hydrogen peroxide strip group experienced a greater reduction in yellowness (Δb*) compared to placebo. The adjusted means and standard errors for Δb* were -4.59 ± 0.23 for the hydrogen peroxide strip group and -0.66 ± 0.23 for placebo strips (Table 2). For lightness, adjusted means and standard errors for ΔL* were 2.33 ± 0.23 and -0.28 ± 0.24 for the peroxide and placebo strip groups, respectively. The peroxide strip group also experienced a greater reduction in redness (Δa*) when compared to placebo, with adjusted means and standard errors of -1.20 ± 0.09 and -0.10 ± 0.09, respectively. Groups differed significantly ($P < 0.0001$) with respect to the individual Δb*, ΔL* and Δa* color parameters. With respect to composite whitening, ΔW* mean and standard errors were -4.76 ± 0.27 for the peroxide group and -0.21 ± 0.28 for placebo. As with the individual L*a*b* parameters, groups differed significantly ($P < 0.0001$) with respect to ΔW*.

The scatterplot of two-parameter whitening (Δb* *versus* ΔL*) illustrated the individual whitening response with the active strips and placebo control (Fig. 1). Most of the placebo subjects clustered generally around zero for Δb* and ΔL*. In contrast the overwhelming majority of subjects using 6.5% H_2O_2 gel system experienced two-color parameter (Δb* and ΔL*) improvement with treatment. Digital images demonstrated the overall whitening seen following 21 days use of the 6.5% hydrogen peroxide strips (Fig. 2, v1,v2).

Both treatments were well-tolerated. Adverse events were mild in severity, and did not contribute to any treatment modification or early withdrawal. Mild and transient tooth sensitivity was the most common adverse event (Table 3).

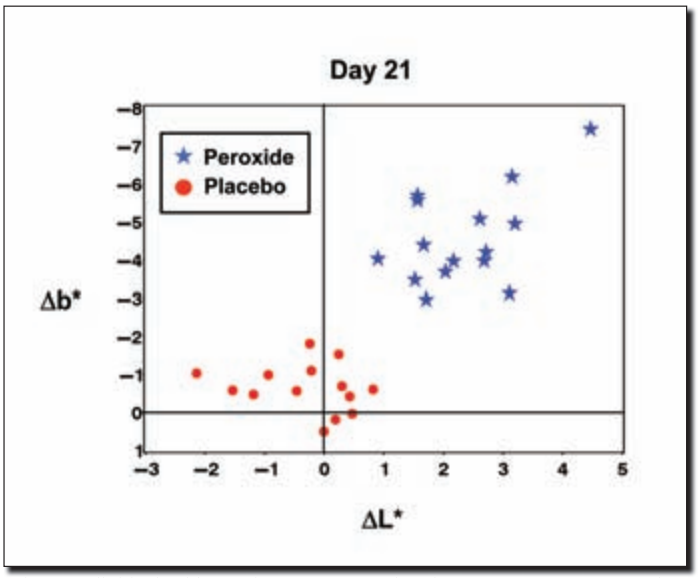

Fig. 1. Individual subject color response: Color change at Day 21, scatter plot (Δb* & ΔL*) by subject and group.

Table 3. Possible or probable treatment related oral irritation or tooth sensitivity.

AE source/ AE classification	Peroxide strip (n = 15) Subject # (%)	Placebo strip (n = 15) Subject # (%)	Overall (n = 30) Subject # (%)
Self reported			
Oral irritation	1 (6.7)	1 (6.7)	2 (6.7)
Tooth sensitivity	4 (26.7)	0 (0)	4 (13.3)
Observed			
Oral irritation	2 (13.3)	1 (6.7)	3 (10.0)

Four subjects in the 6.5% hydrogen peroxide strip group (27% of that group) reported tooth sensitivity at some time during the 21-day treatment period. There were no reports of tooth sensitivity in the placebo group. Two subjects (one in each group) reported mild oral irritation. Clinical examinations were generally unremarkable.

Discussion

In this randomized, double-blind, placebo-controlled study, where efficacy was measured objectively *via* digital image analysis, use of 6.5% hydrogen peroxide whitening strips yielded significant improvement in all color parameters measured in the study. Use of the fixed, low-dose (13 mg of hydrogen peroxide) strips was well-tolerated. Relative to placebo, tooth sensitivity represented the only appreciable adverse event seen with the peroxide strip. These events were infrequent in occurrence, transient in duration, and mild in severity. No subjects modified or discontinued strip application due to a treatment-related adverse event.

Results from this study confirm earlier reports of significant color change following use of 6.5% hydrogen peroxide whitening strips.[12,13,16-18] Unlike these previous studies, which involved peroxide-based trays or strips as positive experimental controls, this new research was placebo-controlled. Placebo-controlled clinical trials are widely recognized as playing an important role in biomedical research, because causality can be directly inferred from studies of this nature. With respect to methods, the measured placebo response in this trial was low overall, with the adjusted mean

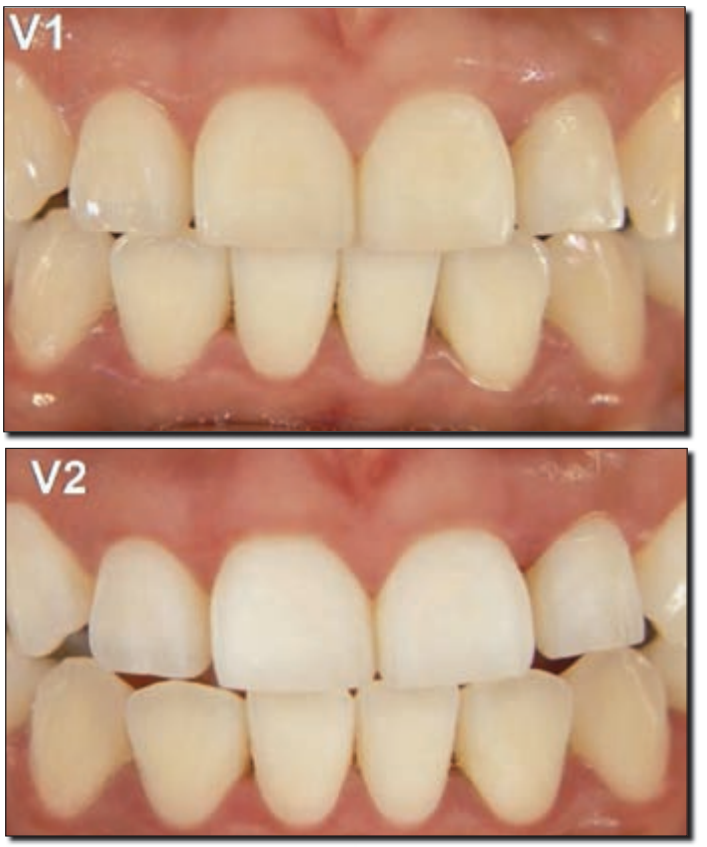

Fig. 2. Color change over time, 6.5% H_2O_2 strips. (V1) Baseline image; (V2) Image after 21-day use of 6.5% H_2O_2 strips.

composite color change (ΔW*) approaching zero. The finding of a near-zero placebo response (where one should exist) provides additional evidence of the merit of using digital images to assess change in tooth color in randomized clinical trials.

Use of the 6.5% hydrogen peroxide strips for 21 days resulted in visible color change evident in the digital images collected as part of the research. For the primary endpoint, Δb*, the magnitude of improvement was considerable, with subjects in the peroxide strip group averaging a nearly 4-unit reduction in yellowness (Δb*) *versus* placebo after 3 weeks. Such response, while impressive, is consistent with a previous meta-analysis of more than 600 subjects who participated in strip-based clinical trials, where age and tooth color were both shown to impact clinical response.[22] The new university-based research was conducted in a population age 20-30 with appreciable discoloration. Clinical improvement following use of the 6.5% hydrogen peroxide strips was consistent with that expected given the presenting conditions at baseline.

a. The Procter & Gamble Company, Cincinnati, OH, USA.
b. Fuji Photo Film Co., Tokyo, Japan.

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Daytime use of a custom bleaching tray or whitening strips: Initial and sustained color improvement

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ABSTRACT: Purpose: To compare the clinical response of 6% hydrogen peroxide whitening strips and a 10% carbamide peroxide custom tray system under common daytime usage conditions, in an Italian dental research center. **Methods**: Informed consent and baseline measurements were collected, and 43 healthy adults were randomly assigned to 6% hydrogen peroxide whitening strips (Crest Whitestrips) or the 10% carbamide peroxide custom tray (Opalescence 10%). The maxillary arch was treated twice daily for 30 minutes at-home. Treatment was discontinued after 2 weeks, and subjects were monitored for an additional 4 weeks. Efficacy (initial and sustained) was measured objectively from standard digital images of the maxillary facial tooth surfaces using the international CIELAB system. Safety was assessed from interview and examination. Treatments were compared after 2 weeks (end-of-treatment) and 6 weeks (4 weeks post-treatment) using analysis of covariance methods. **Results**: Both groups exhibited color improvement at the Week 2 end-of-treatment visit. For yellowness, mean (SD) Δb^* at Week 2 was -2.10 (0.70) for the strip group and -1.61 (1.03) for the tray group. For lightness, mean (SD) ΔL^* at Week 2 was 1.25 (0.92) for the strip group and 1.17 (1.19) for the tray group. Compared to Week 2, the strip group retained 89-92% of the initial Δb^* and ΔL^* color improvement at Week 6 (4 weeks post-treatment), while the tray group had 80-90%. Groups differed significantly ($P < 0.05$) on end-of-treatment and post-treatment Δb^*, favoring the strips. Both daytime treatments were well-tolerated, with minor tooth sensitivity and oral irritation representing the most common findings. (*Am J Dent* 2007;20:19A-22A).

CLINICAL SIGNIFICANCE: Daytime use of a 6% hydrogen peroxide strip and a 10% carbamide peroxide tray both resulted in tooth whitening, with significant reduction in yellowness favoring the strip system initially after 2 weeks and sustained over a 4-week post-treatment period.

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Introduction

Various factors are recognized to contribute to internal (intrinsic) tooth discoloration, including injury, antibiotic use, fluorosis and aging.[1] The relationship between age and tooth color is particularly well established, with aging contributing to measurable changes in the yellowness and brightness of tooth color.[2] Since the 1980s, topical application of peroxide to tooth surfaces has been recognized to improve intrinsic tooth color and to whiten teeth.[3] Treatment is commonly administered at-home, using one of the various hydrogen or carbamide peroxide professional or direct-to-consumer systems.[4]

Peroxide concentration and contact time affect whitening response. Instrumental measurement of tooth color shows higher concentrations and longer contact times yield more whitening.[5] Barrier systems (trays or strips) extend contact time. In the absence of a barrier, use of relatively high peroxide concentration gels results in little incremental whitening, probably because of insufficient contact time for the peroxide diffusion.[6]

While peroxide degradation may occur rapidly, the use of a custom bleaching tray with a reservoir can extend some peroxide delivery over a period of several hours.[7] Extensive daytime tray wearing was impractical, so most of the early systems were tested and used overnight. Always more popular, daytime treatment has become more prominent since the advent of easy-to-use whitening strips in 2000.[8] This hydrogen peroxide strip system is now the most popular approach, with millions of users, and considerable clinical research evidence on safety and effectiveness when used for 30 minutes twice daily at various concentrations and treatment durations.[4,9-14]

Some patients will not accept overnight usage, so overnight tray systems commonly include labeling for day use. How effective are overnight tray systems when used during daytime? Clinical response with shorter usage, in theory, may be readily predicted from known peroxide degradation curves.[15] Accordingly, this clinical study was conducted to compare the whitening efficacy and safety of daytime hydrogen peroxide whitening strips to a marketed professional custom tray-based bleaching system used during the day. The research focused, in part, on whether the measured efficacy of the daytime tray regimen could be predicted from kinetic data on peroxide degradation during tray use.

Materials and Methods

This was a prospective, randomized, parallel, examiner-blind study conducted in Livorno, Italy. The research protocol and informed consent were reviewed and approved by an institutional review board prior to study initiation. The study population (43 subjects) was limited to generally healthy adults 18 years of age and older with no history of tooth whitening and no current tooth sensitivity. After informed consent, eligibility was determined, and baseline measurements were collected. A maxillary impression was taken, and stone casts were prepared for the purpose of fabricating a custom bleaching tray with reservoirs following manufacturer's instructions.

Balancing for baseline demographics and tooth color, subjects were randomly assigned (1:1) to either the 6% hydrogen peroxide whitening strip (Crest Whitestrips[a]) or 10% carbamide peroxide custom tray (Opalescence 10%[b]) groups.

Table 1. Baseline demographic characteristics and color parameters.

Baseline characteristic/ Statistic	Strips (n=21)	Tray (n = 22)	Overall (n = 43)	Two-sided P-value
Age (Years)				
Mean (SD)	32.0 (11.24)	33.7 (11.69)	32.8 (11.37)	0.6238
Minimum-maximum	19 – 56	19 – 55	19 – 56	
Gender				
Female	16 (76.2%)	13 (59.1%)	29 (67.4%)	0.3319
Male	5 (23.8%)	9 (40.9%)	14 (32.6%)	
Tobacco use				
No	15 (71.4%)	15 (68.2%)	30 (69.8%)	1.000
Yes	6 (28.6%)	7 (31.8%)	13 (30.2%)	
Coffee/tea/cola drinker				
No	0 (0.0%)	2 (9.1%)	2 (4.7%)	0.4884
Yes	21 (100.0%)	20 (90.9%)	41 (95.3%)	
b* (Yellow-blue)				
Mean (SD)	17.3 (1.72)	17.1 (1.69)	17.2 (1.69)	0.7005
Mininum-maximum	14.2 – 21.2	14.4 – 20.0	14.2 – 21.2	
L* (Lightness)				
Mean (SD)	75.0 (2.46)	74.1 (2.15)	74.5 (2.32)	0.2179
Mininum-maximum	67.0 – 79.1	69.4 – 78.1	67.0 – 79.1	
a* (Red-green)				
Mean (SD)	6.6 (0.78)	6.7 (0.68)	6.6 (0.72)	0.6008
Mininum-maximum	5.2 - 9.2	5.7 - 7.7	5.3 – 9.2	

Subjects were instructed to apply their assigned product, either the 10% carbamide peroxide tray (approximately 3-3.5% hydrogen peroxide) or the 6% hydrogen peroxide whitening strips on the maxillary arch, for 30 minutes twice daily, following manufacturers' instructions. Treatment was unsupervised at-home over a 14-day period.

Because of the dissimilar delivery systems, test products were supplied in blinded kit boxes. Subjects assigned to the strip group received one carton of 28 maxillary whitening strips in foil pouches, while subjects in the tray group received 10 syringes of tooth bleaching gel, a custom tray, and case. Each kit also contained three tubes of anticavity toothpaste (Crest Cavity Protection[a]), two extra-soft manual toothbrushes (Crest[a]), and an instruction sheet.

Efficacy and safety were evaluated at baseline, Week 2 (end-of-treatment) and Week 6 (4 weeks post-treatment). Effectiveness was measured from change in tooth color using standard digital images of the maxillary teeth. This objective color measurement method has been used to demonstrate peroxide concentration and time effects for whitening strip and tray systems.[5,10] In use, subjects were positioned in a chin rest, and retractors were inserted to allow easy visualization of the anterior facial dentition. Images were then captured under standard, bilateral polarized lighting conditions using a high resolution digital camera and zoom lens connected to a personal computer. This measurement system was calibrated relative to color standards daily, prior to use, and again hourly during use. Safety was assessed from clinical examination and interview at each post-baseline visit. The oral examination included an evaluation of the oral and perioral regions. All clinical and instrumental measurements were blind as to treatment assignment.

After clinical evaluation, a standard program was used to identify "tooth" pixels in each digital image. Red-green-blue values were determined for each maxillary anterior tooth pixel relative to the calibration standard. Values were averaged and transformed to international CIELAB three-dimensional color space as b* (yellow – blue), L* (light – dark), and a* (red – green).[16] Changes in yellowness (Δb*) and brightness were derived by comparing the post-treatment values to baseline. A whitening benefit was represented by negative Δb* (yellowness reduction), and positive ΔL* (increasing lightness). One endpoint, Δb*, was selected *a priori* as primary because of the relevance of this parameter to personal color perception.[17]

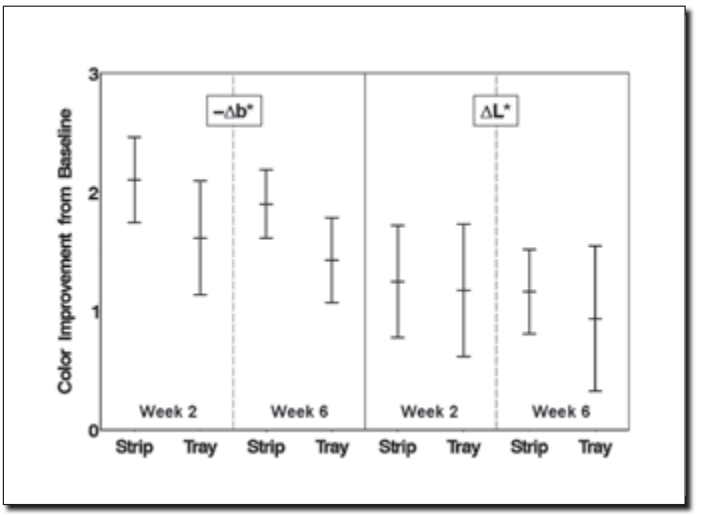

Figure. Mean and 95% confidence intervals for tooth color improvement (−Δb* and ΔL*), end-of-treatment (Week 2) and post-treatment (Week 6).

Color improvement was determined using the mean color change from baseline within each treatment group and then performing one-sample *t*-tests. Groups were compared using (ANCOVA) methods. The response was color change from baseline and the covariates were baseline color and age. Nonlinear regression analysis was used to model both peroxide degradation and whitening effectiveness over time. All comparisons were two-sided at a 5% level of significance. Adverse event data, including tooth sensitivity and oral irritation, were summarized overall and by treatment group.

Results

Forty-three subjects were randomized and treated with one of the two test products. The study population ranged in age from 19-56 years, with a mean (SD) age of 32.8 (11.4). Females accounted for two-thirds of participants, with tobacco use (30%) and coffee/tea/dark cola consumption (95%) being common. Groups were balanced at baseline with respect to pertinent demographic and behavioral parameters as well as starting tooth color (Table 1). Six subjects (four in the strip group and two in the tray group) missed the 2-week visit, while one additional subject (in the tray group) missed the Week 6 visit.

Both groups exhibited color improvement at the Week 2 end-of-treatment visit (Figure). For yellowness, mean (SD) Δb* at Week 2 was -2.10 (0.70) for the strip group and -1.61 (1.03) for the tray group. For lightness, mean (SD) ΔL* at Week 2 was 1.25 (0.92) for the strip group and 1.17 (1.19) for the tray group. Both groups differed significantly ($P < 0.001$) from baseline with respect to the b* and L*. At Week 6 (4 weeks post-treatment), both treatments continued to exhibit significant color improvement relative to baseline. For yellowness, mean (SD) Δb* at Week 6 was -1.90 (0.56) for the strip group and -1.43 (0.74) for the tray group. For lightness, mean (SD) ΔL* at Week 6 was 1.16 (0.69) for the strip group and 0.94 (1.27) for the tray group. As with end-of-treatment (Week 2), both groups differed

Table 2. ANCOVA treatment comparisons (Δb* & ΔL*) at Weeks 2 and 6.

Visit/treatment group	N	Change from baseline: Adjusted mean change (SE)	Treatment comparison: Treatment difference (SE)	Treatment comparison: Two-sided P-value
Δb* (Yellow-blue)				
Week 2				
Strips	17	-2.09 (0.169)	-0.470 (0.230)	0.0494
Tray	20	-1.62 (0.156)		
Week 6				
Strips	17	-1.87 (0.131)	-0.425 (0.180)	0.0245
Tray	19	-1.45 (0.124)		
ΔL* (Lightness)				
Week 2				
Strips	17	1.30 (0.260)	0.170 (0.358)	0.6384
Tray	20	1.13 (0.239)		
Week 6				
Strips	17	1.20 (0.242)	0.305 (0.337)	0.3720
Tray	19	0.90 (0.228)		

significantly (P< 0.003) from baseline with respect to b* and L* at Week 6. At both Week 2 and Week 6, response was more variable with the daytime tray compared to the strip system based on the 95% confidence intervals shown in the Figure.

Both groups exhibited appreciable color retention during the post-treatment period (Table 2). Adjusted mean (SE) Δb* for the strip group was -2.09 (0.17) and -1.87 (0.13) at Week 2 and Week 6, respectively. For comparison, adjusted mean (SE) Δb* for the tray group was -1.62 (0.16) at Week 2, and -1.45 (0.12) at Week 6. Groups differed significantly in Δb* at the end-of-treatment (P= 0.049) and post-treatment (P= 0.025) time points. Adjusted mean (SE) ΔL* for the strip group was 1.30 (0.26) and 1.20 (0.24) at Week 2 and Week 6, respectively, compared to 1.13 (0.24) and 0.90 (0.23) for the tray group. Groups did not differ significantly in ΔL* at either time point (P> 0.37).

Oral irritation (23% of subjects) was the most common adverse event overall. Occurrence was similar in the two groups, with five subjects in the strip group and five subjects in the tray group reporting irritation some time during the study. Tooth sensitivity (12%) was less common. All adverse events were minor in severity and transient in duration. Most oral irritation and tooth sensitivity resolved during treatment, or following treatment completion. No subjects modified or discontinued product usage due to an adverse event, and all adverse events were shown to have resolved at the time of the post-treatment examination.

Discussion

A clinical trial was conducted in a private dental research center in Livorno, Italy, to compare 6% hydrogen peroxide whitening strips and a 10% carbamide peroxide custom tray bleaching system. Initial treatment response was measured after 2 weeks of daytime use from standardized digital images of the anterior dentition. In this research, both groups showed significant (P< 0.03*)* color improvement after 2 weeks daytime use. Keeping contact time constant (twice per day for 2 weeks), color improvement (Δb* and ΔL*) was 29% greater with the higher concentration strips compared to the lower concentration tray. Groups differed significantly (P< 0.05) on end-of-treatment Δb*.

Whitening response was measured again 4 weeks post-treatment to assess color stability. Both groups showed appreciable color retention during this post-treatment period. Compared to Week 2, the strip group retained 89-92% of the initial Δb* and ΔL* color improvement at the Week 6 (4-week post-treatment) visit, while the tray group had 80-90%. Like end-of treatment, groups differed significantly (P< 0.03) on post-treatment Δb*, favoring the strips.

Both daytime treatments were well-tolerated, with minor tooth sensitivity and oral irritation representing the most common findings. These were mild in severity, and limited to the treatment period only. There were no persistent product-related adverse events during the post-treatment monitoring period, and no subjects discontinued or reduced treatment early because of an adverse event.

Previous research[18,19] showed the 10% carbamide peroxide tray system to improve tooth shade or color under conditions of overnight use. Few studies have evaluated objective color change with the 10% carbamide peroxide tray under shorter, daytime usage conditions. Interestingly, the clinical response seen for the daytime tray was well-predicted from the area-under-the-curve kinetic profile for this carbamide peroxide gel and its known clinical response with overnight use. Previous research described peroxide availability over time for this 10% carbamide peroxide system.[15] Using the mean in-tray peroxide concentration, the percent concentration was calculated relative to the mean concentration at 0 hours where the concentration was measured out to 10 hours. A non-linear model was used to fit the kinetic profile of the tray product.

$$\% \text{ Concentration (hours)} = \alpha\, e^{-\beta\,(\text{hours})} + \gamma, \text{ where}$$

$$\alpha \pm SE = 82.0 \pm 9.4,\ \beta \pm SE = 0.375 \pm 0.115,\ \gamma \pm SE = 13.4 \pm 8.2$$

Only α and β were significant (P< 0.05) terms in the model. This kinetic profile function was then integrated from 0 to t_0 hours to yield the concentration × time area-under-the-curve (AUC):

$$AUC\ (\text{hours}) = (\alpha/\beta)\,(1 - e^{-\beta\,(\text{hours})}) + \gamma(\text{hours})$$

With this formula, 30 minutes use twice daily would yield a daily concentration × time AUC of 88.2. The cumulative 2-week AUC, then, was calculated by multiplying the daily AUC by 14 treatment days. This AUC was then modeled using whitening outcomes from a previous study involving the same 10% carbamide peroxide tray system used overnight for 14 nights.[20] That study of 11 subjects measured at 3, 7, 10, and 14 days, used the same methods as this new study in Italy. A non-linear model was constructed to approximate the effectiveness (Δb*) of the tray system under conditions of daytime use, based on the expected AUC for that product with daytime use:

$$\Delta b^* \cong \theta\,(1 - e^{-\lambda\,(AUC)})$$

where $\theta \pm SE = -3.88 \pm 0.56$, $\lambda \pm SE = 0.000538 \pm 0.000185$

Both θ and λ were significant (P< 0.006) terms in the model. Used twice daily for 30 minutes, the 10% carbamide peroxide tray group was expected to yield a -1.88 Δb* after 14 days. In the Italy trial, we observed an unadjusted mean Δb* of -1.61, approximately 86% of the effect predicted by the kinetic/clinical models. While the discrepancy was small, more research would be needed to ascertain whether population or other factors could be used to further refine these estimates.

This clinical trial compared two marketed whitening systems under common, daytime usage conditions. For one of the treatment groups, the 6% hydrogen peroxide whitening strips, there are numerous reports of color improvement with daytime use.[12,17,21] This new study confirms these earlier clinical findings, and extends the evidence to include treatment and evaluation within a dental practice setting in Italy. For the other group, the 10% carbamide peroxide tray system, most published reports are confined to overnight use and/or outcomes measured using the more subjective shade guide method. There is some evidence of efficacy for this lower concentration tray system with 2 hours continuous use over a 2-week period.[10] The new study demonstrated significant ($P < 0.01$) color improvement for the 10% carbamide peroxide gel under the more convenient conditions of short-term daytime use.

Under head-to-head testing conditions, the strip system yielded significant ($P < 0.05$) reduction in yellowness compared to the custom tray, at both end-of-treatment and post-treatment monitoring. There were a number of differences between treatments, including peroxide type (hydrogen or carbamide peroxide), concentration (3.5 or 6% hydrogen peroxide equivalent), barrier (strip or tray), peroxide dose (12 mg or 40+ mg), and others.[22] Causality cannot be determined from multi-variable research of this nature. Any of the various product differences (and combinations) may have contributed to the response observed in this research. What can be concluded is that under common use conditions, the lower total dose, uniformly thin gel whitening strips yielded superior whitening initially and over time after treatment. Color response of the daytime tray could be reasonably predicted from peroxide kinetics and preceding clinical data. Finally, the similar rate of color retention for strip and tray whitening suggests a common mechanism, in this case peroxide-based oxidation, for these two delivery systems.

a. The Procter & Gamble Co., Cincinnati, OH, USA.
b. Ultradent Products, Inc., South Jordan, UT, USA.

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Clinical trial of long-term color stability of hydrogen peroxide strips and sodium percarbonate film

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ABSTRACT: Purpose: To compare initial and sustained clinical response of 6% hydrogen peroxide whitening strips and a 19% sodium percarbonate film in a randomized controlled trial. **Methods**: Informed consent was obtained, after which 72 subjects were randomized to 6% hydrogen peroxide whitening strips (Crest Whitestrips), 19% sodium percarbonate brush-applied gel that dries as a film (Crest Night Effects), or placebo brush-applied gel without peroxide. Efficacy (digital imaging) and safety (clinical examination and interview) were assessed after 2 weeks treatment, and again at up to eight post-treatment timepoints over an 18-month post-treatment period. **Results**: For Δb* (yellowness), end-of-treatment adjusted means ± standard errors (SE) were -2.37 ± 0.088 for the strip group, -1.36 ± 0.091 for the film group, and -0.08 ± 0.090 for the placebo group. For ΔL* (brightness), end-of-treatment adjusted means ± SE were 2.40 ± 0.121 for the strip group, 1.47 ± 0.125 for the film group, and 0.06 ± 0.122 for the placebo group. Groups differed significantly ($P < 0.02$) at end-of-treatment and throughout post-treatment. All treatments were well-tolerated, both peroxide-containing systems exhibited appreciable color retention throughout the 18-month post-treatment period, and there were no meaningful, persistent adverse events seen with long-term follow-up. (*Am J Dent* 2007;20:23A-27A).

CLINICAL SIGNIFICANCE: This randomized controlled trial provided evidence of initial tooth color improvement, post-treatment color stability, and extended safety for two peroxide-containing systems (strip and film) evaluated over an 18-month period.

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Introduction

The use of peroxides for tooth whitening represents perhaps the most common esthetic procedure in dentistry worldwide. Introduced in the late 1980s as "nightguard vital bleaching", the technique involved fabrication of a custom mouthguard (tray) to carry a 10% carbamide peroxide gel to tooth surfaces.[1] Treatment was typically overnight (hence "nightguard") over a period of several weeks. Adverse events were primarily tooth sensitivity and/or oral irritation relating to the peroxide gel or the carrier tray.[2] Most of the adverse experiences resolved during or soon after the bleaching process, usually without any special intervention or treatment. While the adverse events were transient, tooth whitening was more durable. In clinical trials, shade change may be measured over several months or years, depending on the population, treatment, and other factors.[3,4]

The advent of whitening strips[5] represented a major departure from conventional tray-based treatment. The flexible polyethylene strips carried a uniform thin hydrogen peroxide gel directly to tooth surfaces without fabrication of a custom tray. This unit-dose approach was an easy-to-use alternative for daytime tooth whitening. Various strip systems have been introduced at concentrations ranging from 5-14% hydrogen peroxide, depending on gel thickness.[6,7] Initial clinical response with strips is reportedly similar to that seen with the custom bleaching trays.[8] Post-treatment monitoring has demonstrated that color durability persists over at least a 6-month period.[9]

After whitening strips, other peroxide delivery systems were developed focusing on the area of convenience. One of these, a 19% sodium percarbonate whitening system, was developed to deliver peroxide within an anhydrous silicone polymer suspension.[10] Applied with a brush to a dry tooth surface at night, the suspension forms an enamel-adherent substantive film that slowly releases peroxide with hydration. In clinical trials,[11,12] overnight use of this 19% sodium percarbonate film over a 2 to 6-week period resulted in initial color improvement and sustained color retention after treatment completion. Controlled clinical research was conducted to compare initial color improvement and long-term color retention following use of 6% hydrogen peroxide whitening strips and the 19% sodium percarbonate film.

Material and Methods

A randomized, placebo-controlled trial was conducted to compare initial color response of two different peroxide-containing whitening systems with treatment, and long-term post-treatment color retention after completion of treatment. The target population was generally healthy adults from the metropolitan Berlin, Germany area who desired to have their teeth whitened. Eligible subjects were randomly assigned to one of three treatment groups: 6% hydrogen peroxide whitening strips (Crest Whitestrips[a]), 19% sodium percarbonate brush-applied gel that dries to a film (Crest Night Effects[a]), or placebo brush-applied gel without peroxide (the negative experimental control). Subjects were evaluated after 2 weeks treatment, and again at up to eight post-treatment timepoints over an 18-month period.

Prior to study initiation, the study protocol, informed consent and recruitment plans were reviewed and approved by an institutional review board (Charité Ethics Committee, Berlin, Germany). Inclusion in the study was limited to healthy adults with at least 16 natural teeth, including four maxillary incisors with a pretreatment tooth shade score of A2

Table 1. Baseline demographics and behavioral characteristics.

Baseline characteristic	Strips (N=24)	Film (N=24)	Placebo (N=24)	Overall (N=72)	P-value
Age (years)					
Mean (SD)	29.4 (7.66)	31.8 (10.64)	28.8 (7.39)	30.0 (8.66)	0.4621
Range	19 - 51	18 - 60	19 - 51	18 - 60	
Sex (%)					
Female	17 (70.8%)	17 (70.8%)	18 (75%)	52 (72.2%)	1.000
Male	7 (29.2%)	7 (29.2%)	6 (25%)	20 (27.8%)	
Tobacco use (%)					
No	16 (66.7%)	15 (62.5%)	16 (66.7%)	47 (65.3%)	1.0000
Yes	8 (33.3%)	9 (37.5%)	8 (33.3%)	25 (34.7%)	
Coffee/tea/cola consumption (%)					
No	3 (12.5%)	3 (12.5%)	1 (4.2%)	7 (9.7%)	0.6860
Yes	21 (87.5%)	21 (87.5%)	23 (95.8%)	65 (90.3%)	

or darker to allow for broad inference of study results. Individuals with prior bleaching history, current sensitivity, or acute dental treatment needs were excluded from the study. Subjects were randomly assigned to one of the three treatment groups, balancing for baseline tooth color and age, since these factors are known to impact clinical response.[6]

Subjects were assigned 2 weeks treatment with hydrogen peroxide whitening strips, sodium percarbonate film, or placebo. Individuals in the strip group received 28 maxillary and 28 mandibular whitening strips for twice daily treatment, while individuals in the percarbonate film and placebo groups received 14 individual sachets and 14 applicator brushes for overnight use. Products were dispensed in a blinded subject kit box, with written instructions for use. For the strip group, subjects were instructed to apply strips twice daily for 30 minutes, treating the maxillary and mandibular arches separately over a 14-day period. Subjects in the film and placebo groups were instructed to brush first, dispense the test product on the brush applicator, and then apply it to the facial surfaces of the maxillary and mandibular anterior teeth at bedtime for 14 nights. First use was supervised for all groups. Subsequent treatment was at-home and unsupervised. In addition to the test products, each test kit (strip, film or placebo) contained an anticavity dentifrice (Blend-a-Med Cavity Protection Toothpaste[a]) and soft toothbrush (Oral-B 40 Soft Bristle[a]) to standardize oral hygiene.

Efficacy and safety were assessed after completion of maxillary and mandibular treatment for all groups (end-of-treatment) and again at post-treatment Months 1, 2, 3, and 6. Subjects were resupplied with the anticavity dentifrice and soft toothbrushes throughout the first 6-month post-treatment monitoring period to continue standardized oral hygiene. At the end of the 6-month period, subjects in the placebo group were discharged from the research, and provided a marketed whitening system for at-home treatment. Informed consent was obtained from subjects in the two peroxide groups for long-term evaluation. With the examiners still blinded as to treatment, these subjects (strip and film groups) were evaluated at post-treatment Months 12, 15, 16, and 18. During the last 12 months of post-treatment monitoring, oral hygiene was not standardized.

Standard digital images were collected at all visits to assess effectiveness. This objective, instrumental method had sufficient measurement sensitivity to detect a peroxide concentration response for the different tooth whitening systems.[8,13]

Table 2. Number of subjects per visit and treatment.

Visit	Strips	Film	Placebo	Overall
Baseline	24	24	24	72
End-of-treatment	24	23	24	71
Month 1	24	23	24	71
Month 2	24	23	24	71
Month 3	23	22	23	68
Month 6	24	22	24	70
Month 12	17	15		32
Month 15	17	14		31
Month 16	16	13		29
Month 18	17	15		32

Using this method, images were captured under polarized light with high resolution digital camera (Fuji HC Series 3CCD[b]), 1:2.8/12-96 mm zoom lens and personal computer. Color measurements were calibrated to known standards each day prior to use and hourly thereafter. Red-green-blue average values were obtained for the 12 anterior teeth. These average values were transformed to yield CIELAB tooth color values for b* (yellow – blue), L* (lightness), and a* (red – green).[14] Color change was calculated for each subject by subtracting the color at each visit from baseline, where $\Delta b^* = b^*_{visit} - b^*_{baseline}$ and $\Delta L^* = L^*_{visit} - L^*_{baseline}$. Tooth whitening was characterized by decreased Δb^* (reduction in yellowness) and increased ΔL^* (increased brightness).[6]

Safety was assessed from clinical examination and interview at each post-baseline visit. A directed clinical examination of the oral and perioral region was conducted to ascertain any signs of adverse changes to teeth or supporting structures. The interview focused on tooth sensitivity or oral irritation during treatment, since these represent the most common adverse events associated with vital bleaching.[2] Both the clinical examination and interview were conducted blind to treatment assignment. Onset, severity and duration of adverse events were collected.

Fisher's exact test was used to assess group balance for gender and behavioral parameters, while two sample *t*-tests were used for age and baseline tooth color. Color change from baseline was tested using paired difference *t*-tests. Between-group comparisons used ANCOVA, with baseline color and age serving as covariate factors. Post-treatment color response was investigated using general linear repeated measures modeling of Δb^* and ΔL^*. A restricted maximum likelihood method of estimation was used to obtain F-tests and confidence intervals based on asymptotic normal theory while the between-visit covariance structure assumed compound symmetry. All comparisons were two-sided at a 5% level of significance. Subject interview and oral examination results were summarized overall and by group.

Results

A total of 72 subjects from the greater Berlin metropolitan area were randomized equally to the strip, film and placebo groups. Mean (SD) age at baseline was 30.0 (8.66) years, ranging from 18-60. Of these, 72% of subjects were female, while 35% used tobacco daily. Treatment groups were balanced (P> 0.46) on baseline demographics and behavior parameters (Table 1).

With respect to subject disposition, 71 subjects (99% of

Table 3. Treatment comparisons at end-of-treatment and Month 6.

Treatment	N	Baseline mean	Adjusted mean change from baseline (SE)	P-value *vs*. film	P-value *vs*. placebo
Δb* End-of-treatment					
Strips	24	18.98	-2.37 (0.088)	<0.0001	<0.0001
Film	23	18.99	-1.36 (0.091)		<0.0001
Placebo	24	19.15	-0.08 (0.090)		
Δb* Month 6					
Strips	24	18.98	-2.18 (0.085)	<0.0001	<0.0001
Film	22	19.03	-1.06 (0.090)		<0.0001
Placebo	24	19.15	-0.04 (0.087)		
ΔL* End-of-treatment					
Strips	24	74.61	2.40 (0.121)	<0.0001	<0.0001
Film	23	74.15	1.47 (0.125)		<0.0001
Placebo	24	74.46	0.06 (0.122)		
ΔL* Month 6					
Strips	24	74.61	2.37 (0.113)	<0.0001	<0.0001
Film	22	74.10	1.46 (0.120)		<0.0001
Placebo	24	74.46	0.20 (0.113)		

the population) completed the end-of-treatment visit, and 70 (97%) completed the Month 6 post-treatment evaluation (Table 2). All placebo subjects were discharged at Month 6. Informed consent was obtained from 32 subjects in the remaining two groups (17 subjects in the strip group and 15 subjects in the film group). All 32 of these subjects who were evaluated at post-treatment Month 12, completed the 18-month evaluation.

Treatment groups were well balanced with respect to baseline tooth color (P> 0.48). At end-of-treatment, the strip and film groups differed significantly (P< 0.0001) from baseline with respect to tooth color, while the placebo group did not exhibit any appreciable color change from baseline (P> 0.25). All subjects (100%) in the strip group and most (96%) in the film group exhibited two-parameter color improvement on the anterior teeth. In contrast, there was no evidence of treatment effect for the placebo group, with individual responses distributed around zero. Results were generally similar at post-treatment, with all subjects (100%) in the strip group continuing to exhibit two-parameter color improvement 6 months after treatment completion. At each post-treatment visit over the 18-month period, the strip and film groups differed significantly (P< 0.0001) from baseline with respect to both Δb* and ΔL*.

Between-group comparisons showed significant (P< 0.0001) differences between all three groups at the end-of-treatment visit and the Month 6 post-treatment visit (Table 3). For Δb* (yellowness), end-of-treatment adjusted means ± standard errors (SE) were -2.37 ± 0.088 for the strip group, -1.36 ± 0.091 for the film group, and -0.08 ± 0.090 for the placebo group. For ΔL* (brightness), end-of-treatment adjusted means ± SE were 2.40 ± 0.121 for the strip group, 1.47 ± 0.125 for the film group, and 0.06 ± 0.122 for the placebo group. At Month 6, the Δb* adjusted means ± SE were -2.18 ± 0.085 for the strip group, -1.06 ± 0.090 for the film group, and -0.04 ± 0.087 for the placebo group. Month 6 adjusted means ± SE for ΔL* were 2.37 ± 0.113 for the strip group, 1.46 ± 0.120 for the film group, and 0.20 ± 0.113 for the placebo group. Lastly, the strip and film groups differed significantly (P< 0.02) throughout post-treatment up to and including Month 18 for Δb* and ΔL*.

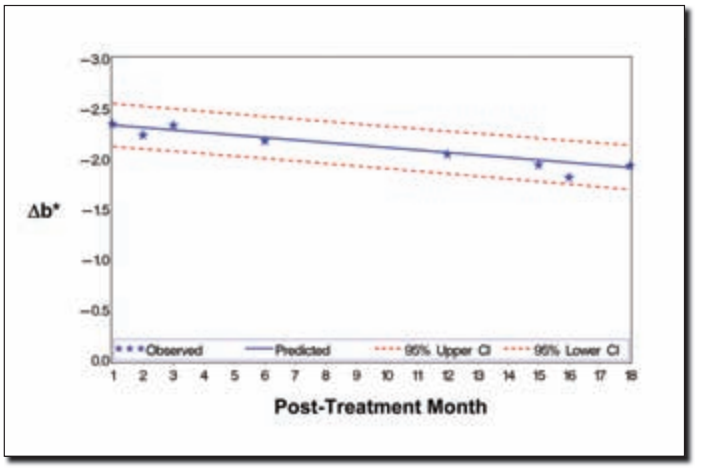

Fig. 1. Post-treatment tooth color (Δb*) response and 95% confidence intervals for the strip group.

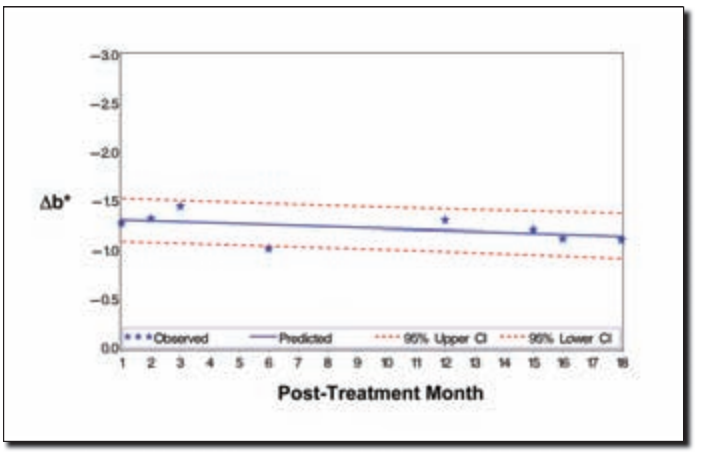

Fig. 2. Post-treatment tooth color (Δb*) response and 95% confidence intervals for the film group.

Post-treatment color response was modeled separately for Δb* and ΔL* to assess long-term post-treatment color retention for the each of the two peroxide groups. Figures 1 and 2 display the observed means for Δb* as well as the predicted means and 95% confidence intervals from the model for each of the peroxide containing groups. A significant (P< 0.0001) linear rebound was observed for Δb* for each group during post-treatment, with a model correlation of 0.76 among these visits. In the strip group, post-treatment Δb* observed means were -2.19, -2.06, and -1.94 at Months 6, 12, and 18, respectively, retaining 82% of the whitening effectiveness by Month 18. Likewise for the film group, the post-treatment Δb* observed mean at Month 18 remained 86% of the whitening effectiveness. In Figures 3 and 4, similar reductions were observed with 91% of the end-of-treatment mean ΔL* still being retained in the strip group and 81% being retained in the film group at the Month 18 visit. Of the 32 observed Δb* and ΔL* means in Figs. 1-4, 31 means (96.9%) were within the predicted 95% confidence intervals.

Tooth sensitivity and oral irritation were the most common adverse events, with strip use most commonly implicated. These adverse events were typically symptomatic only, and confined to the treatment period. There were no new or persistent adverse events during the post-treatment monitoring period. No subjects discontinued use early due to treatment-related adverse events.

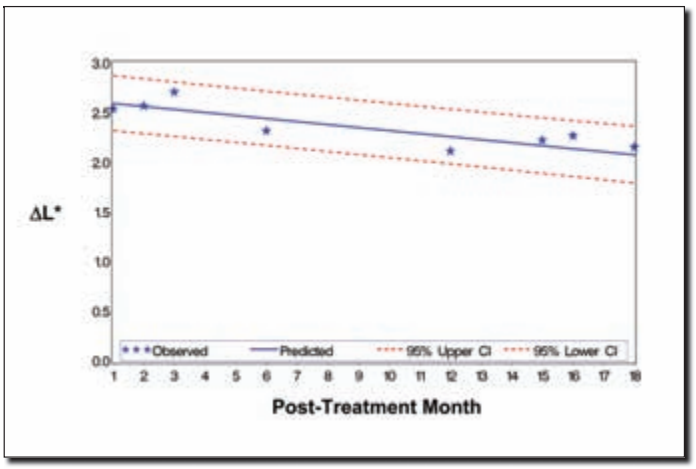

Fig. 3. Post-treatment tooth color (ΔL*) response and 95% confidence intervals for the strip group.

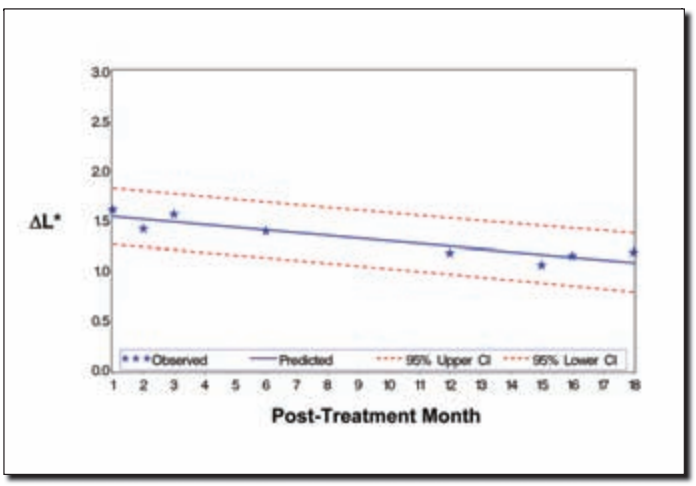

Fig. 4. Post-treatment tooth color (ΔL*) response and 95% confidence intervals for the film group.

Discussion

A randomized, placebo-controlled clinical trial was conducted to evaluate initial color improvement and long-term color retention with two marketed whitening systems. The target population was healthy adults with no history of tooth whitening. After 2 weeks treatment, both of the peroxide-containing groups (strips and brush-applied film) had significant ($P< 0.001$) initial whitening (Δb* and ΔL*). Relative to baseline, twice daily use of the 6% hydrogen peroxide strips for 2 weeks resulted in adjusted means ± SE of -2.37 ± 0.088 for Δb* and 2.40 ± 0.121 for ΔL*, while overnight use of the 19% sodium percarbonate film for 2 weeks resulted in adjusted means ± SE of -1.36 ± 0.091 for Δb* and 1.47 ± 0.125 for ΔL*. Treatments were generally well-tolerated. Previous research showed significant color improvement for the 6% hydrogen peroxide strips or 19% sodium percarbonate film relative to positive or negative controls.[11,12,15,16] In the new head-to-head testing, groups differed significantly from placebo and each other ($P< 0.0001$) with respect to end-of-treatment Δb* and ΔL*, favoring the whitening strips.

This study offered a new perspective on long-term color retention following bleaching. Preceding evidence has been largely confined to longer term shade assessment after overnight use of 10% carbamide peroxide in a custom bleaching tray, sometimes after extended treatment of atypical populations.[3,4,17,18] Fewer studies[19-22] evaluated post-treatment shade retention for higher peroxide concentrations or non-tray delivery systems. Differences in baseline conditions, treatments, methods, and other factors may impact on the degree to which such studies can be generalized. Relatively few studies[9,11,23] have used objective, instrumental methods to assess color stability, and these have been largely confined to weeks or months after completion of treatment. In this new research, post-whitening color retention was measured objectively from digital images collected over an 18-month period. Appreciable color retention, ranging from 81-91% of the initial Δb* and ΔL* changes, was evident for both peroxide-based products at Month 18. Color degradation was both minimal and linear, and readily predicted from modeling. Interestingly, only one of the 32 observed means for Δb* and ΔL* (3%) fell outside the predicted 95% confidence intervals, demonstrating the accuracy to which repeated measures modeling fits the observed efficacy data. This controlled clinical research, perhaps the longest study of its kind, establishes the extended color benefit associated with these two novel peroxide delivery systems.

In this research, the 6% hydrogen peroxide whitening strips exhibited superior whitening initially, and throughout post-treatment monitoring compared to the brush-applied film. Unlike the brush-on gel, all subjects in the 6% hydrogen peroxide group experienced two parameter (Δb* and ΔL*) color improvement at end-of-treatment. All strip subjects continued to demonstrate a two-parameter color improvement 6 months post-treatment. While both peroxide-containing whitening "intensives" had starting hydrogen peroxide-equivalent concentrations exceeding 5%, these systems differed appreciably with respect to the gel formulation, regimen, and other factors. Any of these may have contributed to the differences in whitening seen at end-of-treatment or throughout the post-treatment period. Importantly, only the strip system used a fixed barrier (strip) to maintain peroxide concentration over time. Since only the strip used a fixed barrier, differences in residence time of the peroxide gel under a strip *versus* the brush-applied film may have contributed to the relative clinical response of these two peroxide-containing products.

There was little evidence of a placebo response. At end-of-treatment, the placebo group had adjusted means ± SE of -0.08 ± 0.090 for Δb* and 0.06 ± 0.122 for ΔL*, while at Month 6 (the last visit for the placebo group), adjusted means ± SE were -0.04 ± 0.087 for Δb* and 0.20 ± 0.113 for ΔL*. The placebo group did not differ statistically ($P> 0.05$) from baseline on Δb* or ΔL* at either visit. Use of a placebo film was expected to provide little-to-no color change at end-of-treatment. Measured results were consistent with these expectations, both at end-of-treatment, and at Month 6 post-treatment. This provides important evidence of the validity of the digital imaging method for long-term, as well as short term, clinical research.

This randomized controlled trial evaluated clinical response of two peroxide-containing whitening systems after end-of-treatment, and throughout an 18-month post-treatment period. In this research, the 6% hydrogen peroxide whitening

strips yielded significant (P< 0.02) initial whitening relative to baseline, placebo and a 19% sodium percarbonate, brush-applied film. Most (82-91%) of the initial strip color change was retained throughout the 18-month post-treatment period. There were no meaningful adverse events during treatment, or throughout the post-treatment monitoring period. The study demonstrated the feasibility of using objective, instrumental digital imaging for long-term color monitoring following vital bleaching, and provided evidence of color stability and safety for two peroxide containing systems extending over an 18-month period.

a. The Procter & Gamble Co., Cincinnati, OH, USA.
b. Fuji Photo Film Co., Tokyo, Japan.

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Special Issue Article

Randomized clinical trial comparing whitening strips, paint-on gel and negative control

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ABSTRACT: Purpose: To evaluate efficacy and safety of peroxide-containing whitening strips and a paint-on gel relative to a non-peroxide experimental control. **Methods**: After informed consent, 52 healthy adults in Shanghai, China were randomized to one of three treatment groups: 6% hydrogen peroxide whitening strips (Crest Whitestrips), 5.9% hydrogen peroxide paint-on gel (Colgate Simply White), or water rinse which served as a negative experimental control. Strip use was twice daily over 7 days, while the paint-on gel and rinse were used twice daily over 14 days. Efficacy was measured from standard digital images of the maxillary anterior teeth, and safety was assessed from interview and intraoral examination. **Results**: Whitening strips provided the greatest end-of-treatment reduction in yellowness (Δb^*), with adjusted means ± standard errors of -1.72 ± 0.18 for the strip group, -0.48 ± 0.10 for the paint-on gel group, and 0.13 ± 0.09 for the water rinse group. For ΔL^* (lightness), end-of-treatment adjusted means ± standard errors were 1.88 ± 0.21 for the strip group, 0.60 ± 0.15 for the paint-on gel, and -0.10 ± 0.18 for the negative control. Groups differed significantly ($P < 0.007$) with respect to Δb^* and ΔL^* at end-of-treatment, as well as other color parameters. All treatments were well-tolerated. (*Am J Dent* 2007;20:28A-31A).

CLINICAL SIGNIFICANCE: This clinical study demonstrated that 7 days use of a 6% hydrogen peroxide strip-based bleaching system provided superior and meaningful whitening compared to 14-day use of a 5.9% hydrogen peroxide paint-on gel.

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Introduction

Peroxides have been used for vital and non-vital tooth whitening for more than 100 years.[1] Over the past few decades, at-home treatment has become popular, initially using the "nightguard vital bleaching" approach, where a 10% carbamide peroxide gel was applied in a custom-fitted tray overnight for tooth whitening.[2] Shade change may reportedly be achieved over a period of weeks or months, depending on type and degree of staining, with few adverse events other than minor tooth sensitivity and oral irritation.[3]

Various other at-home peroxide-based whitening systems have been forthcoming, including the notable introduction of hydrogen peroxide whitening strips in 2000.[4] That "trayless" system, using a strip as a barrier, reportedly offered distinct advantages with respect to overall peroxide dose, contact time, and ease-of-use compared to other delivery systems.[4] Initial research focused on whitening strips at concentrations up to 6.5%, including a series of randomized clinical trials comparing strips to various marketed or experimental controls.[5-9] A literature review[10] showed the use of whitening strips to be well-tolerated, with transient tooth sensitivity and minor oral irritation being the only common side effects, and these typically resolved during active treatment.

In 2001, a paint-on system was introduced to deliver peroxide topically without use of a barrier. Like applying nail polish, this 18% carbamide peroxide paint-on gel did not use a barrier for tooth whitening.[11] Clinical results[12,13] to date have been ambivalent. Some research has shown subjective shade improvement relative to baseline or non-peroxide controls. In contrast, objective color research failed to show a significant benefit for a barrier-free paint-on gel relative to various positive or negative experimental controls.[14,15]

Table 1. Summary of treatment groups.

Treatment group	Initial concentration (~%)	Regimen	Duration (Days)	Total applications
Whitening strips	6% hydrogen peroxide	Twice daily	7	14
Paint-on gel	5.9% hydrogen peroxide	Twice daily	14	28
Water rinse	0% hydrogen peroxide	Twice daily	14	28

Recently, a new 5.9% hydrogen peroxide paint-on gel version at a near equivalent active peroxide concentration to the original variant was introduced into certain international markets.[16] New clinical research was conducted to evaluate this barrier-free 5.9% hydrogen peroxide paint-on gel relative to positive (6% hydrogen peroxide whitening strips) and negative (water) controls. This clinical research was conducted on mainland China among individuals who had not previously undergone tooth whitening. Because oral hygiene practices, dental care and diet are widely recognized to contribute to tooth discoloration, subjects were treated directly without a dental prophylaxis or other stain removal in order to replicate expected conditions of use in this region.

Materials and Methods

This was a prospective, randomized, examiner-blind, placebo-controlled study conducted at Shanghai Ninth People's Hospital, Shanghai Second Medical University, Shanghai, China. Both the research protocol and informed consent (in Chinese) were reviewed and approved by an institutional review board prior to study initiation. Balancing for baseline age and color, subjects were randomly assigned to peroxide whitening strips (the positive control), paint-on peroxide whitening gel, or water (the negative control). Table 1 summarizes the three treatment groups:

Table 2. Baseline demographic characteristics and color parameters.

Baseline characteristic/ Statistic	Water rinse (n =17)	Paint-on gel (n =17)	Whitening strips (n =18)	Overall (n =52)	Two-sided P-value
Age (Years)					
Mean (SD)	21.35 (4.06)	21.53 (3.87)	22.61 (6.69)	21.85 (5.01)	0.73
Minimum-maximum	18 - 33	18 - 30	18 - 45	18 - 45	
Gender					
Female	16 (94.1%)	16 (94.1%)	16 (88.9%)	48 (92.3%)	0.99
Male	1 (5.9%)	1 (5.9%)	2 (11.1%)	4 (7.7%)	
Tobacco Use (Daily)					
No	17 (100%)	17 (100%)	18 (100%)	52 (100%)	0.99
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
b* (Yellow-blue)					
Mean (SD)	17.37 (1.11)	17.18 (1.04)	17.40 (0.97)	17.32 (1.03)	0.80
Minimum-maximum	15.54 - 20.10	15.25 - 18.73	15.38 - 18.92	15.25 - 20.10	
L* (Lightness)					
Mean (SD)	75.06 (1.76)	75.11 (1.29)	75.06 (1.98)	75.08 (1.68)	0.99
Minimum-maximum	71.29 - 78.14	72.22 - 77.74	68.31 - 77.34	68.31 – 78.14	
a* (Red-green)					
Mean (SD)	6.97 (0.64)	7.08 (0.45)	7.19 (0.48)	7.08 (0.52)	0.47
Minimum-maximum	5.97 - 8.11	6.28 - 7.73	6.30 – 8.32	5.97 – 8.32	

- Crest Whitestrips[a] - 6% hydrogen peroxide for 1 week.
- Colgate Simply White[b] – 5.9% hydrogen peroxide paint-on gel for 2 weeks.
- Qvarzia[c] water rinse - for 2 weeks, 0% peroxide.

For blinding purposes, each subject was provided an identically-appearing kit box labeled only with a unique subject number, and pertinent usage statements required for investigational research. Subjects were supplied with either 14 maxillary whitening strips in blank over-labeled pouches, paint-on gel in an over-labeled 0.34 oz. polypropylene bottle with applicator brush, or two 16.9 fl. oz. polypropylene bottles of water plus a measuring cup for rinsing, depending on group assignment. Each kit also included an anticavity dentifrice (Crest Cavity Protection Regular[a]) and an extra-soft toothbrush (Oral B Ming Dian[a]) to standardize oral hygiene products during the study period.

Efficacy and safety measurements were obtained at baseline and end-of-treatment (Day 15 for the paint-on gel and negative control, Day 8 for the whitening strips). Efficacy was assessed as change in tooth color as measured from standard digital images of the maxillary anterior teeth. This objective and instrumental color measurement method had previously been used to demonstrate a peroxide concentration response for tray and strip whitening systems.[5,17] With this method, subjects were first positioned in a chin rest, retractors were inserted, and standard bilateral illumination of the arch was obtained from two 150-watt lights and linear polarizers. Images were then captured using a photographic system using a high resolution digital camera (Fujinon HC Series 3CCD,[d] A8x12BMD, 1:2.8/12-96 mm zoom lens[d]), and a personal computer. Color measurements were calibrated to known standards daily prior to use and hourly thereafter to assure proper operation.

Safety was assessed by interview and clinical examination at each post-baseline visit. The interview focused on tooth sensitivity or oral irritation during treatment, since these have been recognized as the most common adverse events associated with vital bleaching. The clinical examination, using a dental light, mirror, and gauze, evaluated the oral and perioral regions, including the gingiva, hard and soft palate, oropharynx/uvula, buccal mucosa, tongue, floor of the mouth, labial mucosa, mucobuccal/mucolabial folds, and lips to assess any changes in oral status with treatment.

Baseline and end-of-treatment digital images were analyzed in order to derive red-green-blue values for the six maxillary teeth. These average values were transformed to yield CIELAB tooth color values for b* (yellow - blue), L* (lightness), and a* (red - green).[18] Color change was calculated for each subject by comparing mean color at end-of-treatment to baseline, where $\Delta b^* = b^*_{visit} - b^*_{baseline}$, $\Delta L^* = L^*_{visit} - L^*_{baseline}$, $\Delta a^* = a^*_{visit} - a^*_{baseline}$. Between-group comparisons of color change used ANCOVA, with baseline color as the covariate. All comparisons were tested two-sided at a 5% level of significance. Subject interview and oral examination results were summarized overall and by group.

Results

Fifty-two subjects were randomized to whitening strips (18), paint-on gel (17) or negative control (17). All subjects in the study were Asian non-smokers. The study population was predominantly female (92%) with an age range of 18-45 years. The population exhibited appreciable tooth discoloration at baseline. Groups were balanced on demographic characteristics and L*a*b* tooth color at baseline (Table 2).

All 18 subjects in the strip group completed the research, while two subjects in the paint-on group and one subject in the water rinse group failed to complete the study. End-of-treatment color measurements showed that whitening strips provided the greatest reduction in yellowness (Δb^*) compared to both the paint-on gel and the water control. Adjusted means ± standard errors were -1.72 ± 0.18 for the strip group, -0.48 ± 0.10 for the paint-on gel group, and 0.13 ± 0.09 for the water rinse. The strip group experienced the greatest increase in lightness (ΔL^*) compared to both the paint-on gel and negative control. Adjusted means ± standard errors for ΔL^* were 1.88 ± 0.21 for the strip group, 0.60 ± 0.15 for the paint-on gel, and -0.10 ± 0.18 for the negative control. Groups differed significantly ($P < 0.007$) with respect to Δb^* and ΔL^* at end-of-treatment (Table 3).

The scatterplot of two-parameter whitening (Δb^* *versus* ΔL^*) illustrated the individual whitening response with whiten-

Table 3. Treatment comparisons at end-of-treatment ANCOVA, adjusted for baseline color.

Color/ treatment	N	Adjusted mean change from baseline (SE)	Paint-on gel		Whitening strips	
			Treatment difference (SE)	P-value	Treatment difference (SE)	P-value
Δb*(Yellow-blue)						
Water rinse	16	0.13 (0.09)	0.61 (0.14)	0.0001	1.85 (0.20)	<.0001
Paint-on gel	15	-0.48 (0.10)			1.24 (0.20)	<.0001
Whitening strips	18	-1.72 (0.18)				
ΔL*(Lightness)						
Water rinse	16	-0.10 (0.18)	-0.70 (0.24)	0.0066	-1.99 (0.28)	<.0001
Paint-on gel	15	0.60 (0.15)			-1.28 (0.26)	<.0001
Whitening strips	18	1.88 (0.21)				
Δa*(Red-green)						
Water rinse	16	-0.03 (0.07)	0.11 (0.09)	0.2435	0.65 (0.10)	<.0001
Paint-on gel	15	-0.13 (0.05)			0.54 (0.09)	<.0001
Whitening strips	18	-0.67 (0.08)				
ΔW* (Composite color)						
Water rinse	16	0.15 (0.15)	0.94 (0.21)	0.0001	2.76 (0.30)	<.0001
Paint-on gel	15	-0.79 (0.15)			1.83 (0.30)	<.0001
Whitening strips	18	-2.61 (0.26)				

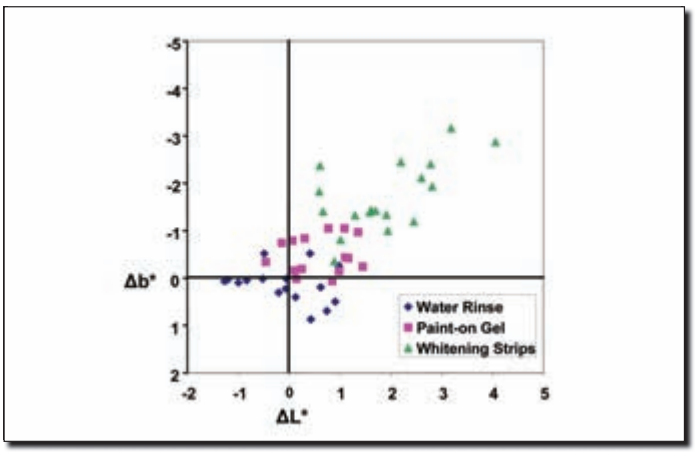

Fig. 1. Individual subject color response: Color change at Day 15, scatter plot (Δb* and ΔL*) by subject and group.

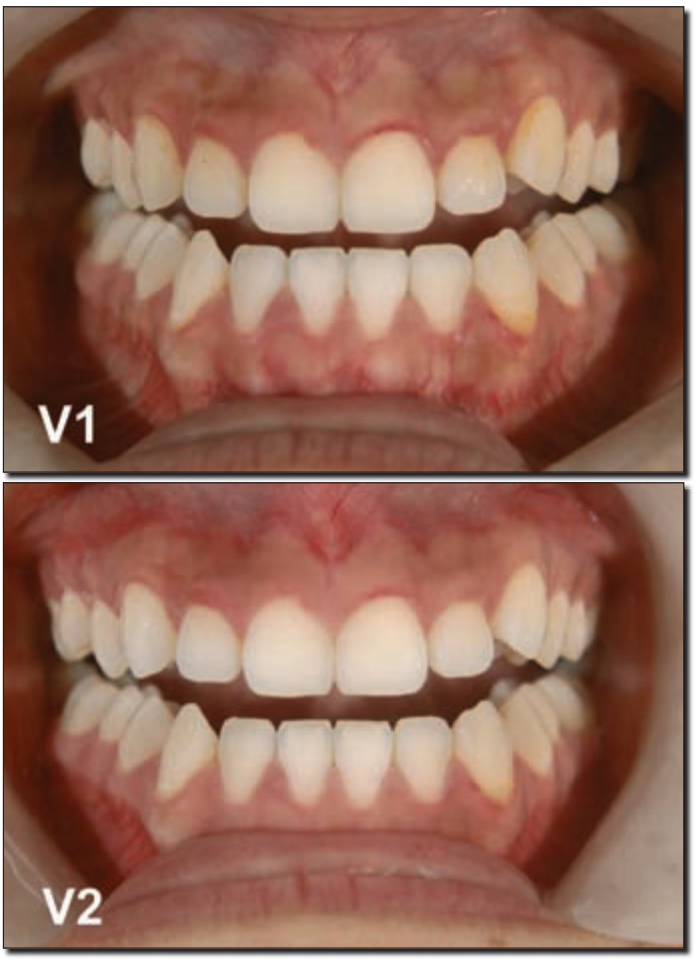

Fig. 2. Color change over time, 6% H_2O_2 strips. (v1) Baseline image; (v2) Image after 7-day use of 6% H_2O_2 strips.

ing strips, paint-on gel and the negative control (Fig. 1). Most of the water rinse subjects clustered generally around zero for Δb* and ΔL*. In contrast, the overwhelming majority of subjects in the whitening strip group experienced two-color parameter (Δb* and ΔL*) improvement with treatment. In addition, the strip group experienced the greatest reduction in red-green (Δa*) compared to both the paint-on gel and negative control. Adjusted means ± standard errors for Δa* were -0.67 ± 0.08 for the strip group, -0.13 ± 0.05 for the paint-on gel, and -0.03 ± 0.07 for the negative control, with the strip group differing significantly ($P< 0.001$) from both the paint-on gel and negative control. Digital images demonstrated the overall whitening seen following 7-day use of the 6% hydrogen peroxide strips (Fig. 2, v1,v2).

All treatments were well-tolerated. Adverse events were mild in severity, and did not contribute to any treatment modification or early withdrawal. Transient tooth sensitivity represented the most common side effect associated with treatment. Occurrence was reported only in the whitening strip group (11% of subjects). Moreover, there were no reports of oral irritation in any treatment group (Table 4).

Discussion

This clinical study involved two marketed hydrogen peroxide whitening systems and a negative control (water rinse) without any hydrogen peroxide. Both peroxide-containing whitening products had similar starting hydrogen peroxide concentrations (approximately 6%). These systems differed appreciably with respect to the presence/absence of a barrier, as only the strip system used a barrier to maintain peroxide concentration over time. The research was conducted in mainland China with a population that had not previously undergone any tooth whitening. Usage followed local norms, and outcomes

Table 4. Possible or probable treatment-related oral irritation or tooth sensitivity.

Adverse event type/source	Water rinse (n =17) Subject # (%)	Paint-on gel (n =17) Subject # (%)	Whitening strips (n =18) Subject # (%)
Self-reported			
Oral irritation	0 (0)	0 (0)	0 (0)
Tooth sensitivity	0 (0)	0 (0)	2 (11%)
Examiner-observed			
Oral irritation	0 (0)	0 (0)	0 (0)
Tooth sensitivity	0 (0)	0 (0)	0 (0)

were measured objectively from standardized digital images of the treated teeth.

At the respective ends-of-treatment, the 6% hydrogen peroxide strip-based bleaching system provided superior whitening compared to the 5.9% hydrogen peroxide paint-on gel or the negative control water rinse. This was evident across all color parameters in the study, where highly significant ($P< 0.0001$) treatment differences always favored the whitening strips. Despite the strip only being applied for one-half the time (7 days *versus* 14), the whitening strip group exhibited more than three-fold improvement in yellowness and lightness compared to the peroxide-containing paint-on gel. These findings confirm an earlier head-to-head study outside of China,[14] where use of whitening strips resulted in significant tooth whitening *versus* paint-on gels.

Notably, there was little evidence of a placebo-like response in the no-peroxide group. After 2 weeks, measured responses for the water rinse group were 0.13, -0.10 and -0.03 for Δb^*, ΔL^* and Δa^*, respectively. Taking all three measures into account, there was no evidence of overall color improvement, as 2 weeks use of the negative control yielded a non-significant ($P= 0.468$) ΔW^* of 0.15. Water rinsing was expected to provide little-to-no color improvement over time. Measured results in this trial were consistent with expectations, providing further evidence of the validity of the digital imaging method in this setting.

For clinicians, this trial demonstrated that starting peroxide concentration and treatment duration may not sufficiently predict whitening clinical response. Despite similarities in starting concentration (~6% hydrogen peroxide), the strip and paint-on gel differed significantly ($P< 0.0001$) on improvement in yellowness, brightness, and redness, as well as overall color improvement. These differences were achieved with one-half the treatment duration (7 *versus* 14 days) for strips compared to the paint-on gel. Since only one of the products used a barrier, differences in residence time of the peroxide gel under a strip *versus* the barrier-free paint-on gel may have contributed to the relative clinical response of these two peroxide-containing products.

a. The Procter & Gamble Co., Cincinnati, OH, USA.
b. Colgate Palmolive GmbH, Hamburg, Germany.
c. Lanzo D'Intelvi, Fonte Paraviso, Italy.
d. Fuji Photo Film Co., Tokyo, Japan.

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Special Issue Article

Clinical trial of tooth whitening with 6% hydrogen peroxide whitening strips and two whitening dentifrices

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ABSTRACT: Purpose: To compare tooth whitening with 6% hydrogen peroxide whitening strips and two whitening dentifrices in a 12-week randomized controlled trial at a Belgian dental school. **Methods:** After informed consent, 46 healthy adults were randomly assigned to one of three strip + dentifrice treatment groups. Subjects received either 6% hydrogen peroxide whitening strips (Crest Whitestrips) and an anticavity toothpaste (Crest Cavity Protection), placebo strips and a sodium fluoride (NaF) whitening dentifrice (Mentadent Whitening Toothpaste) or placebo strips and a sodium monofluorophosphate (MFP) whitening dentifrice (Rembrandt Low Abrasion Whitening Toothpaste). Strip use (peroxide or placebo) was for 30 minutes, twice daily for 2 weeks, while dentifrice use was at least twice daily for 12 weeks. Efficacy was measured from standardized digital images of the maxillary facial tooth surfaces, while safety was evaluated from oral examination and interview. Treatments were compared after 2 weeks (strip use) and 12 weeks (dentifrice use) using analysis of covariance. **Results:** All subjects completed the 12-week evaluation. Adjusting for baseline and age, the peroxide strip group had -2.45 Δb^*, 2.39 ΔL^*, and -0.96 Δa^* at Week 2. Between-group comparisons demonstrated significant ($P < 0.0001$) reductions in yellowness and redness, and increased brightness favoring the peroxide strip group. The peroxide strip group demonstrated 95%+ color retention (Δb^* & ΔL^*) at Week 12, differing significantly ($P < 0.0001$) *versus* either of the continuously used whitening dentifrices. There were no significant ($P > 0.18$) differences between the whitening dentifrice groups at any timepoints. All treatments were well-tolerated, with minor tooth sensitivity and oral irritation representing the most common findings. (*Am J Dent* 2007;20:32A-36A).

CLINICAL SIGNIFICANCE: Twice daily use of 6% hydrogen peroxide whitening strips for 14 days resulted in initial and sustained superior improvement in tooth color compared to either of the whitening dentifrices used continuously for a 3-month period.

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Introduction

Esthetic dentistry represents a prominent and growing part of contemporary dental practice.[1] Several factors have likely contributed to this growth, including improved oral health, changing patient expectations, and media focus. Recent advances in dental materials, including various new restorative materials and techniques, have likely played a complementary role, by improving treatment choices and outcomes.

Tooth whitening, which often represents the entry point for esthetic dentistry, has been the subject of considerable new product research and development in recent years. In the late 1980s, the use of peroxides for so-called "nightguard vital bleaching" allowed for appreciable whitening after a few weeks of overnight tray use.[2] Thereafter, researchers speculated on improvements in popular chemical and abrasive agents to further improve and maintain tooth color.[3] While various new systems were introduced, research and development remained focused on conventional tray-based, at-home tooth whitening.[4] The introduction of easy-to-use whitening strips in 2000 represented a particularly noteworthy and non-traditional development.[5] With an accompanying body of evidence on safety and effectiveness, strip-based whitening grew rapidly to one of the most popular approaches for both professional and self-directed tooth whitening.[6]

After whitening strips, barrier-free peroxide-based systems were introduced as easy-to-use daytime or nighttime options for whitening.[7,8] In head-to-head testing, clinical whitening response with the barrier-free systems was limited relative to popular barrier-based products.[9] Recent comparative research with a peroxide rinse further illustrates that the lack of a barrier may limit the extent of overall tooth color improvement despite use of peroxide.[10]

Commensurate with the introduction of peroxide-based tray systems, a number of so-called "whitening" dentifrices have been marketed.[11] Typically, these whitening dentifrices achieve extrinsic stain removal or "whitening" through physical and/or chemical means. Some utilize improved abrasives or surface acting agents for better physical or chemical surface cleaning.[12] Others may include peroxide, perhaps with a metal catalyst, reportedly to accelerate peroxide activity in the absence of a barrier.[13] Clinical response with these dentifrices may be characterized as preventing new stain deposition or removing existing extrinsic tooth stain at the gingival margin, or elsewhere on the body of the tooth.[14,15] Used daily over extended periods of time, these whitening dentifrices may be cumulative in nature, building slowly over time. This differs from vital bleaching with peroxide, where maximum esthetic response is typically seen at the end of treatment, and color relapses over time.[16] With the differing potential response times for whitening intensive treatments and dentifrices, a 12-week clinical trial was conducted to compare tooth color response head-to-head for a recognized peroxide barrier system (whitening strip) *versus* two marketed whitening dentifrices without peroxide.

Materials and Methods

A randomized, double-blind, placebo-controlled clinical study was conducted to evaluate tooth color (whitening) fol-

Table 1. Summary of treatment groups.

Group	Strip		Dentifrice		
	Type	Peroxide	Type	Fluoride	Abrasive
Peroxide strips	Whitening	6% H_2O_2	Regular	Sodium fluoride	Silica
NaF whitening dentifrice	Placebo	0% H_2O_2	Whitening	Sodium fluoride	Silica
MFP whitening dentifrice	Placebo	0% H_2O_2	Whitening	Sodium mono-fluorophosphate	Alumina

lowing use of a peroxide-based whitening "intensive" treatment, or tooth brushing with whitening dentifrices over a 3-month period. The research protocol, informed consent and related communications were reviewed and approved by the Katholieke Universiteit Leuven Medical Ethics Commission prior to study initiation. Advertising circulars were distributed in the School of Dentistry at the Catholic University of Leuven, Belgium to obtain participants. The study population consisted of generally healthy adults with good oral hygiene, 18 years of age or older, having 16 or more natural teeth. Individuals with meaningful tetracycline staining, fluorosis, tooth sensitivity, fixed orthodontic appliances, or restorations in the anterior dentition were excluded from participation.

Eligibility was determined at the screening visit. At baseline, subjects were randomly assigned to treatment groups, balancing for demographic and tooth color parameters with a whitening intensive applied using a strip, or brushing with one of two whitening dentifrices (Table 1). The whitening intensive group used 6% hydrogen peroxide whitening strips (Crest Whitestrips[a]) and a regular sodium fluoride toothpaste (Crest Cavity Protection[a]). The whitening dentifrice groups were assigned placebo whitening strips without peroxide and one of two whitening dentifrices: a sodium fluoride (NaF) dentifrice with a silica abrasive (Mentadent Whitening Toothpaste[b]), or a sodium monofluorophosphate (MFP) dentifrice with an alumina abrasive system (Rembrandt Low Abrasion Whitening Toothpaste[c]). Strip use (peroxide or placebo) was for 30 minutes twice daily for 2 weeks on the maxillary arch. Subjects were instructed to use their assigned dentifrice (regular or whitening) at least twice daily over a 12-week period.

Test products (peroxide or placebo strips and regular or whitening dentifrices) were supplied in blinded kit boxes. Subjects received 28 maxillary strips in plain foil pouches, three tubes of dentifrice overlabeled in blinded tubes, two soft toothbrushes, and an instruction sheet. The first strip application was supervised using separately-provided placebo strips. Treatment (strip application and brushing) was unsupervised at home.

Subjects were evaluated after 2 weeks of strip use, and again after 12 weeks of toothbrushing. At each visit, effectiveness was measured on the maxillary anterior teeth from standard digital images. Subjects were positioned in a chin rest, retractors were inserted, and images were captured under bilateral polarized lighting using a high resolution digital camera, zoom lens and personal computer.[17] This standard method was calibrated daily prior to use, and again hourly during use relative to color standards. At each visit, safety was assessed by examination and interview to ascertain any adverse events during treatment. Safety and efficacy evaluations were conducted blind to treatment assignment.

Table 2. Baseline demographic characteristics.

Baseline characteristic/ Statistic	Peroxide strips (n = 15)	NaF whitening (n = 16)	MFP whitening (n = 15)	Overall (n = 46)
Age (Years)				
Mean (SD)	22.8 (2.70)	21.1 (1.45)	23.6 (3.31)	22.5 (2.74)
Min.-max.	19 - 29	19 - 23	19 – 31	19 – 31
Sex				
Female: N (%)	9 (60.0%)	10 (62.5%)	10 (66.7%)	29 (63.0%)
Male: N (%)	6 (40.0%)	6 (37.5%)	5 (33.3%)	17 (37.0%)
Tobacco use				
No: N (%)	14 (93.3%)	15 (93.8%)	15 (100.0%)	44 (95.7%)
Yes: N (%)	1 (6.7%)	1 (6.3%)	0 (0.0%)	2 (4.3%)
Baseline b*				
Mean (SD)	17.92 (0.988)	18.19 (1.056)	18.17 (1.290)	18.10 (1.099)
Min.-max.	15.93 - 19.63	15.99 - 19.99	15.77 - 20.19	15.77 - 20.19
Baseline L*				
Mean (SD)	75.90 (1.155)	75.49 (0.993)	75.51 (2.127)	75.63 (1.479)
Min.-max.	73.28 - 77.57	73.99 - 77.40	69.75 - 79.52	69.75 - 79.52
Baseline a*				
Mean (SD)	7.12 (0.388)	7.14 (0.545)	7.24 (0.704)	7.17 (0.550)
Min.-max.	6.60 - 7.91	6.05 - 7.95	6.19 - 8.14	6.05 – 8.14

Digital images were analyzed using a standard process. The red-green-blue camera values were determined for each maxillary anterior tooth pixel relative to the calibration standard, and these values were averaged. Mean RGB values were then transformed to conventional CIELAB three-dimensional color space as b* (yellow–blue), L* (light–dark), and a* (red–green).[18] Changes in tooth color were derived by comparing the post-treatment values to baseline, with meaningful whitening primarily evidenced by a negative Δb^* (yellowness reduction) and positive ΔL^* (increasing lightness).[19]

Tooth color improvement was investigated by calculating the mean color change from baseline for each treatment group and then performing one-sample *t*-tests. Treatments were compared using analysis of covariance (ANCOVA) methods. The response was color change from baseline and the covariates were baseline color and age. All comparisons were two-sided at a 5% level of significance. Adverse event data, including tooth sensitivity and oral irritation, were summarized overall and by treatment group.

Results

A total of 46 subjects signed informed consent and were randomized. Mean (SD) age was 22.5 (2.74) years, ranging from 19-31. There were a total of 29 females and 17 males, and tobacco use was uncommon (4%). The population exhibited considerable range in tooth color at baseline (Table 2). All subjects completed the 12-week evaluation period, and were included in the analyses.

Subjects in the peroxide strip group exhibited the greatest maxillary arch tooth color improvement at Week 2, the end-of-treatment for peroxide and placebo strips. Most subjects (93%) in the peroxide strip group exhibited two-parameter (Δb^* & ΔL^*) improvement in tooth color after 2-week use (Fig. 1). Two-parameter color improvement was less common in either whitening dentifrice group. After 2 weeks, adjusted mean (SE) Δb^* was -2.45 (0.21) for the peroxide strip group, 0.03 (0.21) in the NaF whitening dentifrice group, and -0.37 (0.21) in the MFP whitening dentifrice group (Table 3). Adjusted mean (SE) ΔL^* was 2.39 (0.24), 0.09 (0.24) and 0.58 (0.24) for the peroxide strip, NaF whitening dentifrice, and

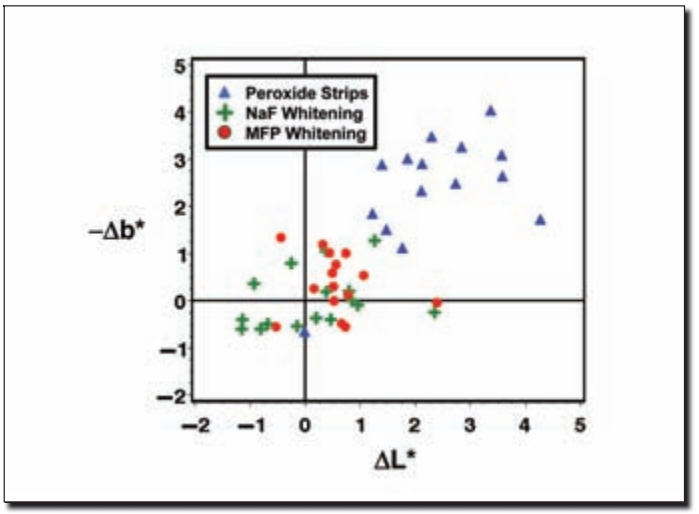

Fig. 1. Scatterplot of -Δb* *versus* ΔL* at Week 2.

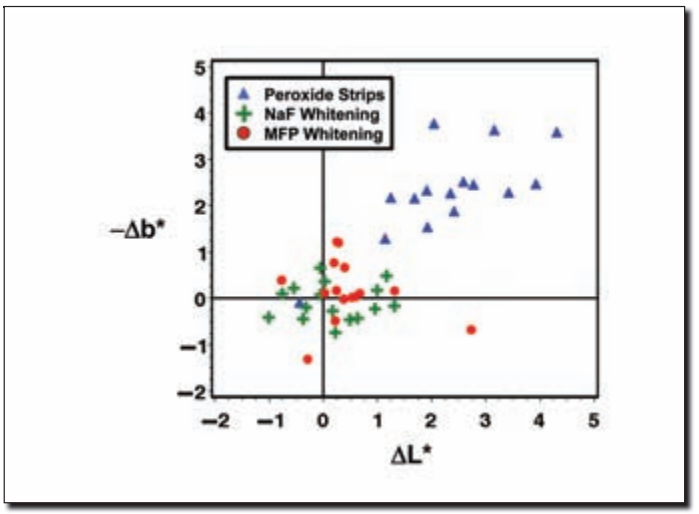

Fig. 2. Scatterplot of -Δb* *versus* ΔL* at Week 12.

MFP whitening dentifrice groups, respectively. Between-group comparisons showed highly significant (P< 0.0001) differences in Δb* and ΔL* for the peroxide strip group compared to either of the whitening dentifrice groups at Week 2. Results were generally similar for change in redness (Δa*), where again, the peroxide strip group differed significantly from the two whitening dentifrice groups at Week 2. The whitening dentifrices did not differ significantly (P> 0.18) on any of the color parameters at Week 2.

At Week 12, the end-of-treatment for the whitening dentifrices, subjects in the peroxide strip group exhibited the greatest overall color improvement. Again, 93% of strip users continued to exhibit two-parameter color improvement 10 weeks after completion of peroxide strip treatment (Fig. 2). Ten weeks after completion of the 6% hydrogen peroxide strips (Week 12), the peroxide strip group exhibited an adjusted mean (SE) of -2.35 (0.18) for Δb* and 2.36 (0.24) for ΔL*. After 12 weeks of toothpaste use, the whitening dentifrice groups had adjusted mean (SE) Δb* of 0.14 (0.18) for the NaF whitening dentifrice, and -0.20 (0.19) for the MFP whitening dentifrice (Table 4). Adjusted mean (SE) ΔL* was 0.15 (0.24) and 0.45 (0.24) for the NaF whitening dentifrice and MFP whitening dentifrice groups, respectively. The peroxide strip group was the only treatment to exhibit a

Table 3. Change in tooth color treatment comparisons at Week 2.

Color /Treatment	N	Adjusted mean change from baseline (SE)	NaF whitening	MFP whitening
Δb*				
Peroxide strips	15	-2.45 (0.207)	< 0.0001	< 0.0001
NaF whitening	16	0.03 (0.210)		0.2001
MFP whitening	15	-0.37 (0.212)		
ΔL*				
Peroxide strips	15	2.39 (0.238)	< 0.0001	< 0.0001
NaF whitening	16	0.09 (0.244)		0.1832
MFP whitening	15	0.58 (0.242)		
Δa*				
Peroxide strips	15	-0.96 (0.106)	< 0.0001	< 0.0001
NaF whitening	16	0.12 (0.107)		0.4865
MFP whitening	15	0.01 (0.108)		

Table 4. Change in tooth color treatment comparisons at Week 12.

Color /Treatment	N	Adjusted mean change from baseline (SE)	NaF whitening	MFP whitening
Δb*				
Peroxide strips	15	-2.35 (0.181)	< 0.0001	< 0.0001
NaF whitening	16	0.14 (0.183)		0.2155
MFP whitening	15	-0.20 (0.185)		
ΔL*				
Peroxide strips	15	2.36 (0.236)	< 0.0001	< 0.0001
NaF whitening	16	0.15 (0.242)		0.3987
MFP whitening	15	0.45 (0.240)		
Δa*				
Peroxide strips	15	-0.63 (0.116)	< 0.0001	< 0.0001
NaF whitening	16	0.34 (0.118)		0.5642
MFP whitening	15	0.24 (0.119)		

Table 5. Possible or probable treatment-related adverse events by type and group, for all subjects, 12 weeks treatment.

Adverse event Type/Source	Peroxide strips (n =15) Subj. # (%)	NaF whitening dentifrice (n =16) Subj. # (%)	MFP whitening dentifrice (n =15) Subj. # (%)
Tooth sensitivity	6 (40.0)	3 (18.8)	0 (0.0)
Oral irritation	1 (6.7)	5 (31.3)	1 (6.7)
Other	0 (0.0)	1 (6.3)	0 (0.0)

reduction in redness (-Δa*) at Week 12. Like Week 2, the peroxide strip group exhibited highly significant (P< 0.0001) improvements in Δb*, ΔL*, and Δa* compared to either whitening dentifrice. The whitening dentifrices did not differ significantly (P> 0.21) from each other for Δb*, ΔL* or Δa* at Week 12.

Adverse events were infrequent, involving 14 subjects (30%), six in the peroxide strip group, seven in the NaF dentifrice group, and one in the MFP dentifrice group. These events were noted during the first 2 weeks, when strips were applied (peroxide or placebo) and dentifrice used, and the subsequent 10-week dentifrice-only phase of the study. Minor and transient oral irritation or tooth sensitivity represented the most common findings (Table 5) during the 3-month study. By group, tooth sensitivity was most common in the peroxide strip group, while oral irritation was most common in the NaF dentifrice group. Other than tooth sensitivity and oral irritation, the only other treatment-related adverse event was a report of transient taste alteration for one subject in the NaF

whitening dentifrice group. Overall, all three treatments were well-tolerated, and no subject discontinued treatment early due to a product-related adverse event.

Discussion

A randomized, placebo-controlled clinical study evaluated the clinical response of 6% hydrogen peroxide whitening strips compared to two whitening dentifrices without peroxide. Peroxide strips were used twice daily for 2 weeks, while the whitening dentifrices were used twice daily over 12 weeks as part of normal oral hygiene. Because of the dissimilar dose forms (strip or dentifrice) and treatment durations (2 or 12 weeks), a double-dummy design was used to ensure blinding. Accordingly, subjects in the peroxide strip group were assigned a regular anticavity dentifrice for use throughout the trial, while subjects in the two whitening dentifrice groups were assigned placebo strips without peroxide. Efficacy comparisons were made using an objective instrumental method that has previously discriminated dissimilar treatments (strip, paint-on gel, dentifrice, tray and/or rinse) in multiple clinical trials.[9,10,17,19,20]

The study in Leuven, Belgium involved adults aged 19-31 with some tooth discoloration. Adjusting for baseline and age, the peroxide strip group had -2.45 Δb^*, 2.39 ΔL^*, and -0.96 Δa^* at Week 2. Between-group comparisons demonstrated significant ($P < 0.0001$) reductions in yellowness and redness, and increased brightness favoring the peroxide strip group. Results were similar at Week 12, which represented 12 continuous weeks of whitening dentifrice use. The peroxide strip group continued to demonstrate significant ($P < 0.0001$) reductions in yellowness and redness, and increased brightness *versus* either of the whitening dentifrice groups. Comparing whitening dentifrice groups, the MFP whitening dentifrice with alumina showed directional color improvement relative to the NaF whitening dentifrice with silica at Weeks 2 and 12. Although the sample size was not adequate to investigate treatment differences of this magnitude, there were no significant ($P > 0.18$) differences between whitening dentifrice groups at any timepoint.

The peroxide strip group was the only treatment to exhibit significant color improvement for both Δb^* and ΔL^*, the two most prominent parameters in personal color perception.[19] In this study, 2 weeks use of the 6% hydrogen peroxide strips yielded a 2.4-2.5 unit improvement in yellowness and brightness. These results were consistent with several other clinical studies where twice daily use of 6% hydrogen peroxide strips over a 14-day period yielded significant improvement in Δb^* and ΔL^*.[19-24] Importantly, this initial color improvement experienced by the strip group at Week 2 was sustained through the 10-week post-strip treatment period. Measured changes were small, with the peroxide strip group retaining at least 96% of initial Δb^* and ΔL^* color improvement. Comparing Week 12 and Week 2, the peroxide strip group had a mean (SD) change in Δb^* of 0.094 (0.762), and a mean (SD) change in ΔL^* of -0.010 (0.713). There was no evidence of significant ($P > 0.64$) color degradation for Δb^* or ΔL^* in the peroxide strip group from Week 2 to Week 12. Initial color improvement, then, was retained over a 10-week period using a regular (non-whitening) anticavity toothpaste and toothbrush for normal oral hygiene.

The strip and dentifrice treatments were well-tolerated. Minor tooth sensitivity and oral irritation were the most common findings. These events, reported in both the peroxide strip and placebo strip groups, were generally mild in severity and resolved during or after strip use. No subjects discontinued or reduced treatment early because of an adverse event.

In head-to-head testing conditions, 14 days use of the 6% hydrogen peroxide whitening strips resulted in meaningful and superior improvement in tooth color compared to either of the whitening dentifrices. Ten weeks following the completion of strip use, the whitening strips continued to exhibit superior color improvement relative to the whitening dentifrices used continuously over a 3-month period. While there was a true strip placebo (no peroxide), this double-dummy trial employed a marketed dentifrice control rather than a placebo dentifrice. Accordingly, there were many possible differences between dentifrices, including the type and amount of dentifrice abrasive, fluoride source, and others. Causality cannot be ascertained from multi-variable research of this nature, since any of these treatment differences (alone or in combination) may have contributed to the response observed in this research. What can be concluded is that the 6% hydrogen peroxide whitening strips yielded superior whitening initially and over time compared to either of the whitening dentifrices. These results are consistent with previous research comparing peroxide-containing whitening strips to whitening dentifrices with or without peroxide.[9,20] Sustained delivery of peroxide *via* the strip barrier likely contributed to the initial and sustained whitening improvement seen with the 6% hydrogen peroxide whitening strips relative to the toothpastes tested in this study.

a. The Procter & Gamble Co., Cincinnati, OH, USA.
b. Unilever, Fabergé, Italy.
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