

## ABSTRACT

**Objective:**  $\Delta E^*$  is commonly used in clinical research to assess overall color change. Because this parameter only reports non-directional, overall color change, mean  $\Delta E^*$  is less sensitive with respect to detecting between-treatment, 3-dimensional ( $\Delta L^*$ ,  $\Delta a^*$ ,  $\Delta b^*$ ) color differences. This research reports an alternative statistical methodology used to simultaneously investigate 3-dimensional color differences between treatments for clinical trials applications.

**Methods:** Data from a randomized, comparative clinical trial involving two bleaching systems (6.0% hydrogen peroxide whitening strips or 10% carbamide peroxide gel/dentifrice/rinse combination system) were analyzed using a repeated measures model. Outcomes were assessed separately at each visit to investigate location differences between the treatments in the 3-dimensional color space ( $\Delta L^*$ ,  $\Delta a^*$ ,  $\Delta b^*$ ).

**Results:** For yellow ( $\Delta b^*$ ), the strip group experienced 0.59, 0.72 and 1.26 unit mean improvements over the combination group, with these treatments differing significantly ( $p < 0.05$ ) at Days 3, 8 and 15 respectively. At Day 15, groups were highly significantly ( $p = 0.0004$ ) different with respect to  $\Delta E^*$ , favoring the 6.0% whitening strip. However, groups did not differ significantly in overall mean color at the intermediary time points Day 8 ( $p = 0.10$ ) or Day 3 ( $p = 0.70$ ) using the conventional  $\Delta E^*$  approach. In contrast, the 3-dimensional ( $\Delta L^*$ ,  $\Delta a^*$ ,  $\Delta b^*$ ) analysis showed highly significant differences between treatments at Day 15 ( $p = 0.004$ ) and at the intermediary time point Day 8 ( $p = 0.007$ ), with directional evidence at Day 3 ( $p = 0.18$ ).

**Conclusion:** Repeated measures modeling of 3-dimensional color differences may provide additional sensitivity to detect overall color differences compared to a two-sample t-test of  $\Delta E^*$ .

## OBJECTIVE

This research reports an alternative statistical methodology used to simultaneously investigate 3-dimensional color differences between treatments for clinical trials applications.

## MATERIALS AND METHODS

A two-week, randomized, parallel group, clinical trial was conducted involving two bleaching systems: 6% hydrogen peroxide whitening strips (Crest Whitestrips™<sup>i</sup>) or 10% carbamide peroxide gel with stock tray/dentifrice/rinse combination system (Rembrandt® Plus™ Superior Bleaching System<sup>ii</sup>). Tooth color was measured objectively using digital image analysis in the CIELab color space as  $b^*$  (yellow-blue),  $L^*$  (lightness), and  $a^*$  (red-green). Color change from baseline was calculated as  $\Delta b^*$ ,  $\Delta L^*$ ,  $\Delta a^*$  with  $\Delta E^* = (\Delta b^{*2} + \Delta L^{*2} + \Delta a^{*2})^{1/2}$ . Efficacy outcomes were assessed separately at each visit to investigate location differences between the treatments in the 3-dimensional color space ( $\Delta b^*$ ,  $\Delta L^*$ ,  $\Delta a^*$ ).

## STATISTICAL MODEL

$$A Y_{ijk} = \mu + \alpha_i + \gamma_j + (\alpha\gamma)_{ij} + \beta_j X_{ijk} + \varepsilon_{ijk}$$

$Y_{ijk}$  = color change from baseline for the  $j$ th color of the  $k$ th subject in the  $i$ th treatment.

$\mu$  = overall mean effect,  $\alpha_i$  =  $i$ th treatment effect,  $\gamma_j$  =  $j$ th color effect.

$(\alpha\gamma)_{ij}$  = interaction of the  $i$ th treatment with the  $j$ th color effect.

$\beta_j$  = slope of the baseline covariate for the  $j$ th color effect.

$X_{ijk}$  = baseline color (covariate) for the  $j$ th color of the  $k$ th subject in the  $i$ th treatment.

$\varepsilon_{ijk}$  = random error for the  $j$ th color of the  $k$ th subject in the  $i$ th treatment.

$i = 1, 2$  corresponding to the strip or tray system (index for the treatment groups).

$j = 1, 2, 3$  corresponding to  $\Delta b^*$ ,  $\Delta L^*$ ,  $\Delta a^*$  (index for the color measurements).

$k = 1, 2, \dots, n_i$ , (subject index within the  $i$ th treatment).

$n_i$  = number of subjects in the  $i$ th treatment group.

A covariance structure was applied to the color effect residuals ( $\varepsilon_{i1k}$ ,  $\varepsilon_{i2k}$ ,  $\varepsilon_{i3k}$ ). Six parameters total were used to model the (unstructured) covariance structure of the within subject color effect. Residuals where either  $i$  or  $k$  differed were assumed to be independent (i.e., subjects were independent of each other and subjects in different treatments were independent).

Model parameters were estimated with restricted maximum likelihood methods implemented in the SAS® MIXED procedure. Means, standard errors, and p-values were calculated for each color dimension using the combined model adjusting for baseline color. A contrast statement was used to test the 3-dimensional hypothesis:

$$H_0: (\Delta b^*_{strip} = \Delta b^*_{tray}) \text{ and } (\Delta L^*_{strip} = \Delta L^*_{tray}) \text{ and } (\Delta a^*_{strip} = \Delta a^*_{tray}) \text{ vs.}$$

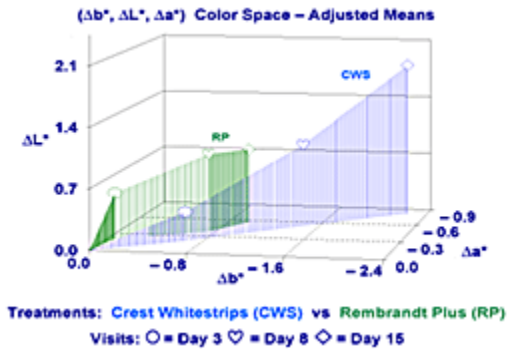
$$H_a: (\Delta b^*_{strip} \neq \Delta b^*_{tray}) \text{ or } (\Delta L^*_{strip} \neq \Delta L^*_{tray}) \text{ or } (\Delta a^*_{strip} \neq \Delta a^*_{tray}).$$

## RESULTS

With respect to yellowness reduction ( $b^*$ ), the whitening strip group experienced 0.59, 0.72 and 1.26 unit mean improvements over the combination group, with these treatments differing significantly ( $p < 0.05$ ) at Days 3, 8 and 15 respectively. The 3-dimensional  $H_0$  contrast comparing mean ( $\Delta b^*$ ,  $\Delta L^*$ ,  $\Delta a^*$ ) between the treatment groups exhibited highly significant differences at Day 15 ( $p = 0.004$ ) and at the intermediary time point Day 8 ( $p = 0.007$ ), with directional evidence at Day 3 ( $p = 0.18$ ). The figure displays the adjusted means from each model by day to illustrate the tooth whitening benefit of the treatments on all color parameters simultaneously. The whitening strip group effectively improves tooth color for all parameters over time, whereas the combination treatment improves  $\Delta L^*$  early on and does not begin to reduce yellowness until Day 8.

3-Dimensional ( $\Delta b^*$ , $\Delta L^*$ , $\Delta a^*$ ) Adjusted Means from each Model by Day			
	Day 3	Day 8	Day 15
Crest Whitestrips	(-0.65, 0.33, -0.21)	(-1.45, 1.00, -0.53)	(-2.23, 1.81, -0.82)
Rembrandt Plus	(-0.06, 0.54, -0.20)	(-0.74, 0.88, -0.38)	(-0.97, 0.88, -0.57)
$H_0$ Contrast p-value	0.1750	0.0066	0.0037

## RESULTS (cont.)



On the other hand,  $\Delta E^*$  measures the distance between a given post-baseline  $L^*a^*b^*$  measurement to the baseline value for each subject and then the mean  $\Delta E^*$  was computed. In the figure,  $\Delta E^*$  represents the average distance from a post-baseline visit to the origin. The treatment groups changed the color of the teeth in completely different ways, however, mean  $\Delta E^*$  was not statistically different ( $p > 0.05$ ) between the treatments at Day 3 or Day 8. At Day 15, groups were highly significantly ( $p = 0.0004$ ) different with respect to  $\Delta E^*$ , favoring the 6.0% whitening strip. This occurred because the magnitude of the mean distance for  $L^*a^*b^*$  from the Day 15 to baseline was much greater for the whitening strip group than the combination group, however,  $\Delta E^*$  does not quantify the between treatment 3-dimensional (directional) differences.

## CONCLUSION

Repeated measures modeling of 3-dimensional color differences may provide additional sensitivity to detect overall color differences compared to a two-sample t-test of  $\Delta E^*$ .

While both treatments were effective in whitening teeth as measured by mean color change from baseline, the whitening strips provided a superior overall whitening response compared to the combination system.

- i. The Procter & Gamble Company, Cincinnati, OH, USA.
- ii. Den-Mat Corporation, Santa Maria, CA, USA.