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Effect of Bleaching Gel Viscosity on Tooth Whitening Efficacy and Pulp Chamber Penetration: An *In Vitro* Study

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Clinical Relevance

The viscosity of the whitening gel or delivery system did not influence efficacy but affected hydrogen peroxide penetration that may relate to increased tooth sensitivity with lower viscosity gels.

SUMMARY

Objectives: Whitening efficacy has been related to hydrogen peroxide (HP) diffusion into tooth structure. However, little information is available relating rheological properties to whitening efficacy. The purpose was to evaluate the whitening efficacy and HP penetration level of a 10% HP gel at three different viscosities and to compare them to a strip delivery system.

Methods and Materials: Extracted molars (n=120) were randomly assigned into five groups (n=24/ group): NC_MED (negative control; median): medium viscosity gel without HP; LOW: 10% HP gel (low viscosity experimental gel, Ultradent Products Inc); MED: 10% HP gel (medium viscosity experimental gel, Ultradent); HIGH: 10% HP gel (high viscosity gel, Ultradent); and CWS: Crest 3D Whitestrips 1-Hour Express (Procter & Gamble). All teeth were subjected to five 60-minute whitening sessions. Instrumental color measurements were performed at baseline (T_0), and 1-day after each application (T_1-T_5), and 1-month after whitening (T_6). HP penetration was estimated with leucocrystal violet and horseradish peroxidase. A Kruskal-Wallis test and *post hoc* Bonferroni test were performed to assess the difference in tooth color change and HP penetration among the groups (α=0.05).

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Results: Hydrogen peroxide penetration levels and overall color changes at T_6 were 0.24 μg/mL / 2.80; 0.48 μg/mL / 8.48; 0.44 μg/mL / 7.72; 0.35 μg/mL / 8.49; 0.36 μg/mL / 7.30 for groups NC, LOW, MED, HIGH, and CWS, respectively. There was a significant difference for HP penetration, while there was no significant difference among the four experimental groups for tooth color change.

Conclusion: Rheological properties should be considered when developing new whitening formulations.

INTRODUCTION

Demand for healthy and beautiful teeth has been building and growing for more than a generation, as the general public envisions and desires a "Hollywood" smile. According to the American Academy of Cosmetic Dentistry, the teeth whitening industry surpassed an annual revenue of $11 billion at the beginning of 2015, with $1.4 billion spent on tooth whitening products.[1] Additionally, statistics show that over 90% of adults believe that a healthy, white smile makes you look more appealing, while over 70% believe that a person's smile can be a critical factor in career advancement.[1] This perception may explain why so many people are willing to invest in teeth whitening. The wide range of whitening modalities available also reflects the high demand: professionally applied in-office whitening; professionally dispensed, patient-applied home whitening; over-the-counter whitening products; and do-it-yourself whitening.[2]

Even though its use is ubiquitous in dentistry around the world and extensively studied, there is a need for further development of innovative and user-friendly whitening systems that are efficient and also safe to use. Studies on diffusion have shown that hydrogen peroxide (HP), which is the primary active agent in most tooth whitening materials, readily penetrates into the pulp cavity in 5 to 15 minutes when applied to the external surface of the tooth.[3,4] The penetration increases with the use of higher peroxide concentration, heat, light, and younger age of the tooth.[4-7] Correlations of HP penetration levels with whitening efficacy did not show any positive relationship.[8]

Most whitening materials are gel-based systems and are manufactured in different viscosities. However, little information is available regarding the effect of rheological properties and delivery systems on tooth whitening effectiveness and HP penetration. Therefore, the purpose of this study was to evaluate the whitening efficacy and hydrogen peroxide penetration level of a 10% HP gel at three different viscosities (low, medium, and high) and also compare them with a strip delivery system. The first null hypothesis tested was that there would be no difference in tooth whitening efficacy regarding overall color change (ΔE*), lightness change (ΔL*), and chroma change in the yellow-blue axis (Δb*) among the different experimental viscosities and delivery systems tested. The second null hypothesis was there would be no difference in HP penetration levels into the pulp cavity among the groups.

METHODS AND MATERIALS

Sample Selection and Preparation

Extracted human molar teeth (n=120) were collected and stored in 0.1% thymol solution (Sigma-Aldrich, St Louis, MO, USA) at 4°C. All teeth were cleaned and checked for the presence of anomalies, caries, existing restorations, crack lines, and severe attrition. The roots were trimmed 2 mm apical to the cementoenamel junction with a sectioning machine (TechCut 4, Allied High Tech Products Inc, Compton, CA, USA). The pulp cavity was enlarged and prepared with tapered diamond burs (NeoDiamond, Microcopy, Kennesaw, GA, USA) toward the lingual with the purpose of establishing an intact labial tooth structure of 2-mm thickness that could contain 50 μL of acetate buffer. The occlusal pits and fissures were sealed with flowable resin (Permaflo, Ultradent Products Inc, Jordan, UT, USA) to prevent any leakage of the buffer out of the cavity. A circular adhesive label 6 mm in diameter was adhered at the center of the labial surface to establish a standardized color reading and whitening area. The remaining tooth was painted with gray nail varnish (Sally Hansen, New York, NY, USA), and then the adhesive label was removed after drying, leaving a standard-sized unpainted area of enamel for whitening application.

Application Protocol by Group

Specimens were randomized into five groups of 24 specimens each, as follows: Group NC_MED (negative control; median): MED viscosity gel without HP (experimental gel, Ultradent) acting as the negative control; Group LOW: 10% HP gel of low viscosity (experimental gel, Ultradent); Group MED: 10% HP gel of medium viscosity (experimental gel, Ultradent), Group HIGH: 10% HP gel of high viscosity (Opalescence GO in syringe delivery, Ultradent), and Group CWS: 10% HP in a strip delivery system

Table 1: *Summary of Whitening Agents Used by Group*

Group	Product	HP Concentration	Viscosity	Lot No
NC_MED	Experimental placebo gel	N/A	Medium	RH1016B
LOW	Experimental bleaching gel	≅ 10%	Low	RH0916A
MED	Experimental bleaching gel	≅ 10%	Medium	GH0916A
HIGH	Opalescence GO 10% HP gel	≅ 10%	High	TQAGL
CWS	Crest Whitestrips 1hr Express	≅ 10%	N/A	6193652600

(Crest 3D Whitestrips 1-Hour Express, Procter & Gamble, Cincinnati, OH, USA). Table 1 summarizes the whitening agents used by group.

A jig was fabricated for each specimen by gently placing the lingual surface of each tooth into an unset increment of polyvinyl siloxane impression material (Aquasil Ultra Heavy, Dentsply Caulk, Milford, DE, USA) at a 30° angle from the base. Whitening material (0.2 mL) was applied on an unpainted enamel surface and covered with a linear low-density polyethylene wrap (Saran Premium Wrap, SC Johnson & Son Inc, Racine, WI, USA) to simulate the placement of a custom fabricated tray (Figure 1). The teeth were kept at room temperature (25°C) during the treatment procedure. All teeth were subjected to a 60-min whitening session for 5 consecutive days and stored in artificial saliva at 4°C throughout the study.[9]

Color Measurement

A contact-type intraoral spectrophotometer (Vita Easyshade Compact Advance, Vita Zahnfabrik, Bad Säckingen, Germany) with a 5-mm diameter probe was used for instrumental color measurements. The Easyshade was calibrated and placed perpendicular and flush to the exposed tooth surface according to the manufacturer's instructions. Measurements were performed seven times each at baseline (T_0), 1 day after each application (T_1 to T_5), and 1 month after whitening (T_6). To standardize the environment, a color-controlled light box (MM 4e GTI Mini Matcher, GTI Graphic Technology Inc, Newburgh, NY, USA) at CIE D_{65}, a color temperature of 6500K, and light intensity of ≈1200 lux was used. Color difference was calculated as ΔE^*_{ab} from the following equation of the Commission Internationale de l'Eclairage:[10]

$$\Delta E^*_{ab} = [(L^*_2 - L^*_1)^2 + (a^*_2 - a^*_1)^2 + (b^*_2 - b^*_1)^2]^{1/2}.$$

Spectrophotometric Assay of HP

HP penetration was measured after the first whitening session and estimated with leucocrystal violet and horseradish peroxidase. Acetate buffer (40 μL) retrieved from the pulp cavity was mixed with 1 mL leucocrystal violet solution (0.5 mg/mL), 0.5 mL of horseradish peroxidase solution (1 mg/mL), and 1 mL of acetate buffer.[11] The final color intensity was measured in an absorbance spectrophotometer (Benchmark, Bio-Rad, Hercules, CA, USA) at a wavelength of 600 nm. A standard calibration curve with known amounts of HP was used to determine the amount in microgram equivalents in the samples.

Measurement of Viscosity

Sample viscosities were measured as a function of shear rate using a stress-controlled rheometer (MCR

Figure 1. *Flow diagram of experimental protocol.*

Table 2: *Color Change (ΔL*, Δb*, and ΔE*) Over Time by Group (Mean±SD)*

Color Change	NC_Med	Low	Med	High	Cws	*P*-value*
ΔL_T1	−0.3±1.4^{Aa}	1.3±2.6^{AC}	1.7±1.5^{AC}	2.0±2.1^{BC}	1.2±3.3^{AC}	<0.001
Δb_T1	0.3±1.3^{A}	−0.6±2.1^{A}	−0.1±2.1^{A}	−0.5±2.1^{A}	0.0±1.9^{A}	0.247
ΔE_T1	1.8±0.9^{A}	3.0±2.2^{A}	2.8±1.4^{A}	3.3±1.71^{A}	3.1±2.5^{A}	0.03
ΔL_T2	1.2±1.7^{A}	3.2±2.6^{A}	2.5±1.7^{A}	2.3±2.0^{A}	1.9±3.4^{A}	0.064
Δb_T2	0.6±1.8^{A}	−1.8±2.3^{B}	−1.5±2.1^{B}	−1.9±1.8^{B}	−1.4±2.1^{B}	<0.001
ΔE_T2	2.5±1.3^{A}	4.4±2.6^{BC}	3.8±1.4^{AC}	3.8±1.6^{AC}	4.1±2.3^{AC}	0.006
ΔL_T3	0.3±1.9^{A}	2.8±2.6^{BC}	1.3±2.9^{AC}	3.2±2.0^{BC}	1.5±3.4^{AC}	<0.001
Δb_T3	−0.9±2.1^{A}	4.0±2.8^{B}	−4.7±2.9^{B}	−4.0±2.4^{B}	−2.9±2.5^{AB}	<0.001
ΔE_T3	2.6±1.6^{A}	5.6±3.1^{B}	5.7±3.2^{B}	5.9±1.8^{B}	5.0±2.3^{B}	<0.001
ΔL_T4	1.5±1.5^{A}	4.5±2.7^{BC}	3.6±2.5^{AC}	4.6±2.1^{BC}	3.2±3.3^{AC}	<0.001
Δb_T4	0.8±2.1^{A}	−3.3±2.6^{B}	−3.8±2.8^{B}	−3.8±2.3^{B}	−3.8±2.0^{B}	<0.001
ΔE_T4	2.7±1.5^{A}	6.1±3.1^{B}	6.0±2.6^{B}	6.7±1.6^{B}	6.0±1.7^{B}	<0.001
ΔL_T5	1.6±1.5^{A}	4.0±2.8^{BC}	3.8±1.6^{BC}	4.1±2.2^{BC}	2.9±3.0^{AC}	<0.001
Δb_T5	0.7±1.6^{A}	−4.6±2.3^{B}	−3.6±2.4^{B}	−4.2±2.2^{B}	−3.8±1.7^{B}	<0.001
ΔE_T5	2.5±1.3^{A}	6.5±3.2^{B}	5.7±2.1^{B}	6.5±2.0^{B}	5.7±1.6^{B}	<0.001
ΔL_T6	1.3±1.8^{A}	5.2±3.2^{BC}	4.0±2.3^{BC}	5.0±2.7^{BC}	3.4±3.2^{AC}	<0.001
Δb_T6	−0.1±2.0^{A}	−5.7±2.8^{B}	−5.8±3.1^{B}	−5.5±3.0^{B}	5.2±2.4^{B}	<0.001
ΔE_T6	2.8±1.4^{A}	8.5±3.2^{B}	7.7±2.9^{B}	8.5±1.8^{B}	7.3±2.2^{B}	<0.001

* *Kruskal-Wallis test.*
[a] *Same letters within a given row indicate no significant differences, based on* post hoc *test adjusted for multiple comparisons.*

301, Anton-Paar GmbH, Graz, Austria) and cone-and-plate geometry with a sandblasted 2°, 25-mm diameter cone at a gap height of 0.052 mm. The rheometer was equipped with an integrated Peltier heating/cooling system and a Peltier hood, to ensure a uniform temperature throughout the sample and minimize evaporation. All tests were performed at a constant temperature of 37°C. Four sets of measurements were conducted on each sample to assess reproducibility, with the data showing an average standard deviation of less than 5%. Flow ramp-up experiments were performed, and sample viscosities were recorded at 37 logarithmically spaced shear rates in the range $\dot{\lambda}$ = 0.1– 400 L/s. The results of the four independent experiments on each sample were averaged to report the viscosity at each shear rate.

Data Analysis

Descriptive statistics were conducted to profile all variables in the study. The Kruskal-Wallis, followed by the *post hoc* Bonferroni test, was performed to determine whether differences in color parameters and change in color parameters among the five groups at each post-whitening time point were statistically different. The change in each color parameter is defined as the difference between baseline and each post-whitening time point. The above-mentioned tests were also performed to assess the difference in HP penetration levels among the groups. Based on the power analysis, a sample size of 22 for each group was determined to have 80% power, with an alpha of 0.05 and effect size of ΔE* = 2.7. IBM SPSS Statistics Version 24 (IBM Corp, Armonk, NY, USA) was used for data analysis at a significance level of 0.05.

RESULTS

Tooth Color

There were no significant differences for baseline color parameters L_0*, a_0*, or b_0* (p=0.687, 0.980, and 0.868, respectively). Color change (ΔL*, Δb*, ΔE*) over time by group is summarized in Table 2. All groups except for NC_MED showed an increase in lightness and decrease in chroma in the yellow-blue axis over time (Figures 2 and 3). ΔL*, Δb*, and ΔE*were not significantly different among the four experimental groups from T_1 to T_6. All groups showed a significant separation from the negative control group at T_3, which persisted until the 1-month follow-up evaluation. Overall color changes at T_6 were 2.80, 8.48, 7.72, 8.49, and 7.30 for groups NC_MED, LOW, MED, HIGH, and CWS, respectively. Figure 4 illustrates the overall color change by group over time.

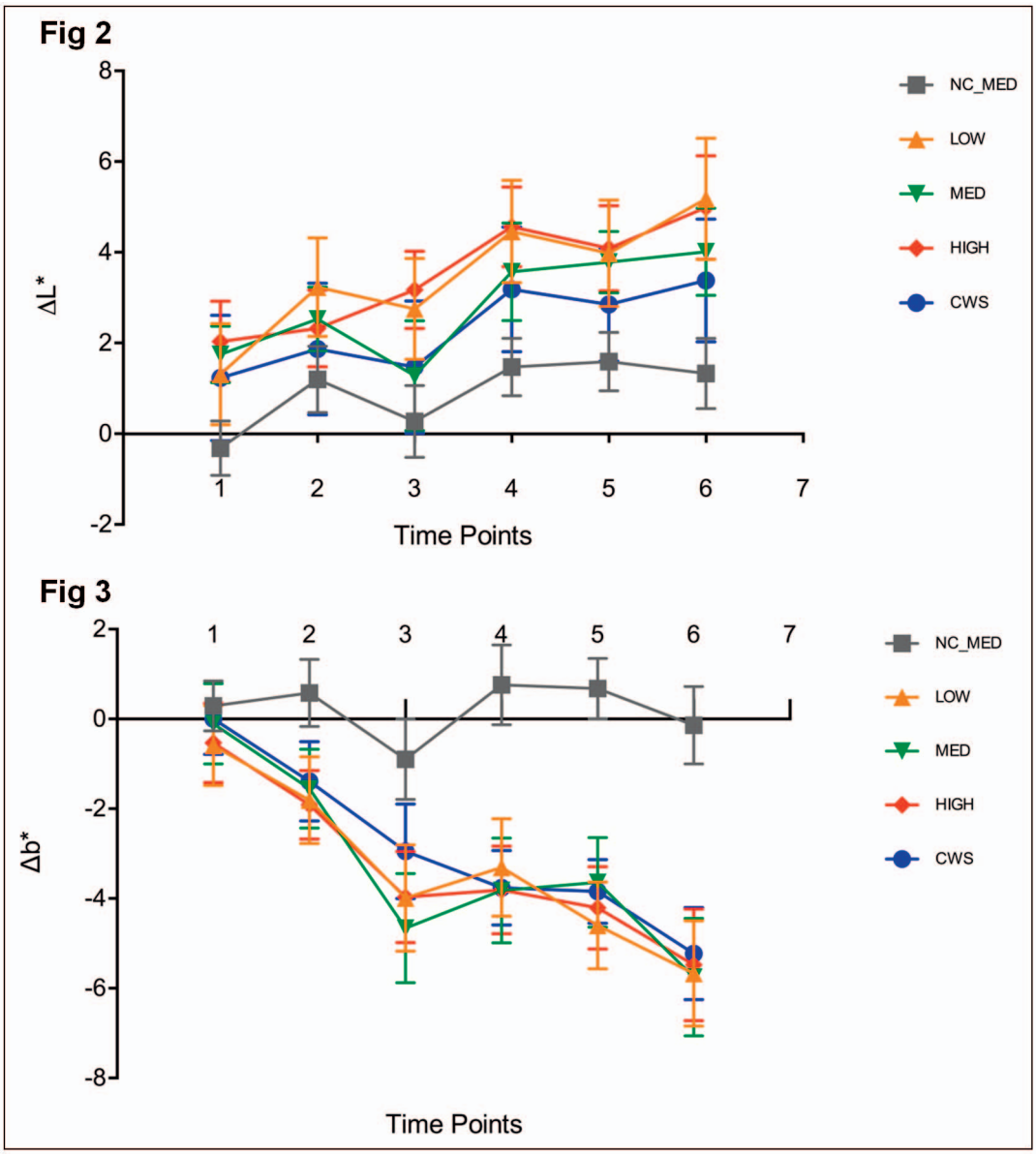

Figure 2. *Line plot of change in lightness* over time by group.*
Figure 3. *Line plot of change in the yellow-blue axis* over time by group.*

HP Penetration

The data provided strong evidence of differences in the distribution of HP penetration among the five groups ($p<0.001$). After we adjusted for multiple comparisons using an overall 0.05 level of type I error, lower HP values were observed for groups NC_MED (median: 0.24 μg/mL), HIGH (0.35 μg/mL), and CWS (0.36 μg/mL), which did not differ from each other ($p>0.05$). Higher HP values were observed for LOW (median: 0.48 μg/mL) and MED (median: 0.44 μg/mL), which were not different from each other, although each differed significantly from the other three groups ($p<0.05$). Figure 5 illustrates the distribution of HP penetration by group by box plots.

Viscosity

Figure 6 shows the average sample viscosity (η) for NC_MED, LOW, MED, and HIGH, plotted against the applied shear rate, $\dot{\lambda}$. All samples show shear thinning behavior described approximately as $\eta \sim \dot{\lambda}^{-0.8}$, with end-point viscosities (viscosity at the highest applied shear rate) of 6.64 Pa·s, 2.16 Pa·s, 4.0 Pa·s, and 14.4 Pa·s for NC_MED, LOW, MED, and HIGH, respectively. The increasing order of

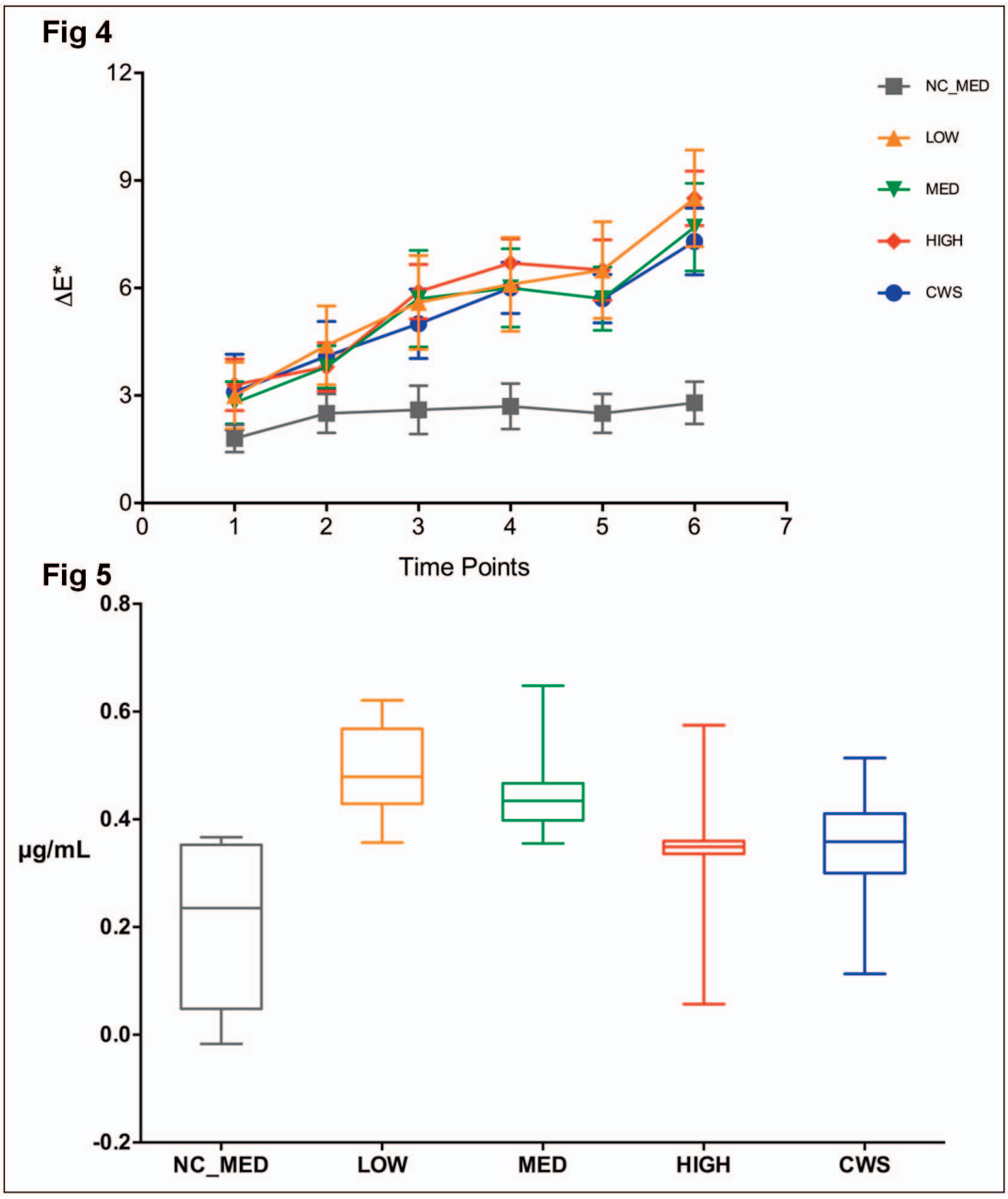

Figure 4. *Line plot of overall color change* over time by group.*
Figure 5. *Boxplots of HP penetration levels (μg/mL) by group.*

sample viscosities for groups LOW, MED, NC_MED, and HIGH can be observed over all shear rates investigated.

DISCUSSION

The oral health care industry is flourishing with a variety of whitening formulations and delivery systems. Nonetheless, the quest for the ideal material demonstrating maximum whitening with minimal adverse effects is ongoing. The current study compared bleaching gels of different viscosities for whitening efficacy and penetration potential into the pulp cavity. The rationale underlying this study was to provide information on the optimum viscosity and delivery system for developing future whitening strategies.

The findings supported our first null hypothesis that there would be no differences in color change among the experimental groups for ΔL*, Δb*, and ΔE* at any time points. Though the results were not

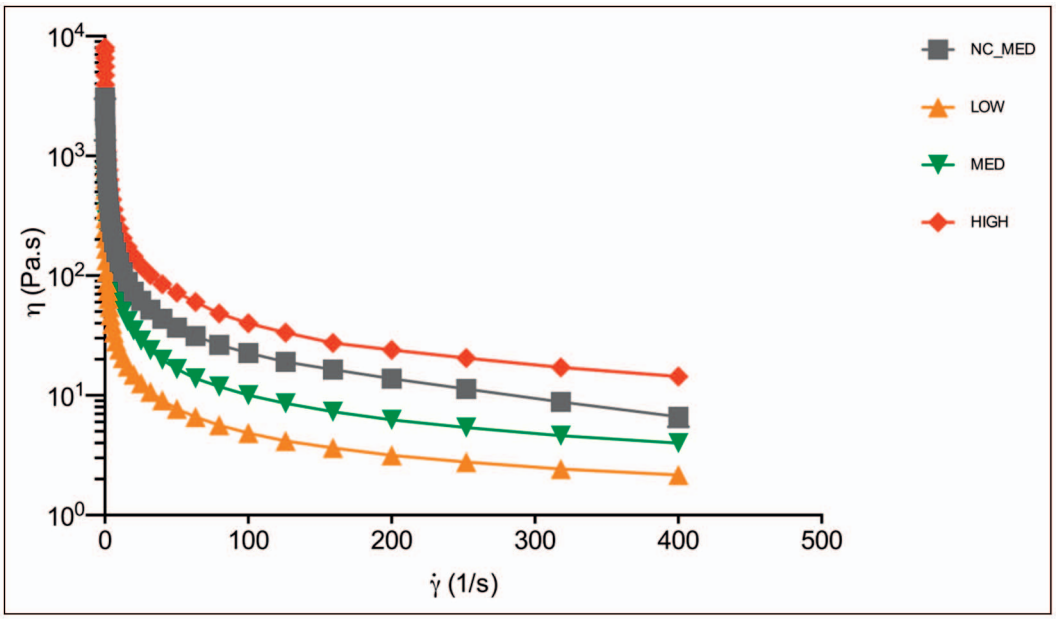

Figure 6. *Line plot of shear rate to viscosity by group.*

surprising, our study was the first to show that viscosity and type of delivery system did not affect whitening efficacy when concentration and exposure time were constant. We used the 50% acceptability threshold of $\Delta E^*=2.7$ to interpret tooth color change results.[12] Professionally dispensed, at-home whitening methods with the ADA Seal of Acceptance continue to use 10% carbamide peroxide in custom-fabricated trays with exposure times of up to 8 hours have shown long-term success rates in terms of efficacy and safety.[13-16] However, it is imperative to note that the trend in the over-the-counter (OTC) market is to promote higher concentrations at shortened exposure times.[17-21] We used 10% HP with an exposure time of 1 hour to relate to instructions of OTC products. According to the International Organization for Standardization (ISO 28399: 2011), a test method for laboratory assessment of whitening efficacy, ΔE^* should be two or greater for the product to be regarded as acceptable.[22] The standards do not indicate a post-measurement time point, but all four experimental groups in this study surpassed the efficacy requirement with simply a single application at 1 day after whitening.

It is evident that HP needs to diffuse from the enamel into the dentin to exert its effect on stain molecules. There are numerous *in vitro* studies quantifying HP penetration under different circumstances.[3-8,23] Still, considering the potentially toxic effects that HP has on the pulp, it is debatable whether a high penetration is desirable for superior whitening efficacy.[24] Attention to the rheological properties of whitening gels was given about withstanding shear stress so that it does not flow out of the tray and is not easily washed away or swallowed.[25] However, there have been no studies relating possible relationships between HP composition and viscosity of the whitening material.

Based on the results, our second null hypothesis was rejected. Notably, there was a difference among the experimental groups with lower viscosity gels (LOW and MED) showing higher penetration levels than the high viscosity gel (HIGH) and the strip delivery system. This is in accordance with another study that evaluated the penetration potential of potassium nitrate, which is a commonly used agent to prevent and manage tooth-whitening-induced sensitivity. The study found that potassium nitrate penetration was influenced by concentration and partly affected by the viscosity and suggested considering these properties for desensitizing formulations.[26]

Penetration studies are limited by not fully representing the dynamic *in vivo* process with a positive pulpal pressure during the whitening process. Additionally, the pulp cavity was enlarged to hold the acetate buffer required to stabilize HP in the pulp cavity. Even so, the current study provided relevant data on the relationship of rheological properties and type of delivery system to whitening efficacy and HP penetration. Future studies are

needed to evaluate the significance of these rheological properties on adverse effects such as gingival irritation, as the penetration of HP into gingival tissue is expected to differ based on viscosity. These findings could inform future strategies for developing whitening formulations with minimal adverse effects and maximum efficacy.

CONCLUSIONS

Within the limitations of this *in vitro* study,

1. Tooth whitening efficacy is not influenced by the rheological properties of the gel or delivery system when exposure time and concentration are kept constant.
2. The level of HP penetration is affected by the viscosity of the material, with lower viscosity materials exhibiting higher penetration levels in the pulp cavity.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of Loma Linda University.

Conflict of Interest

The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service and/or company that is presented in this article.

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