Efficacy of different protocols for at-home bleaching: A randomized clinical trial

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Abstract: Purpose: To evaluate the efficacy of two products used for at-home bleaching with different application times. **Methods:** 80 participants were enrolled and divided into four groups, (1) 10% carbamide peroxide 1 hour a day; (2) 10% carbamide peroxide overnight; (3) 7.5% hydrogen peroxide 1 hour a day; and (4) 7.5% hydrogen peroxide overnight. The duration of treatment was 14 days. Color measurement was performed using a dental spectrophotometer on the right maxillary central incisor and the canine, at baseline and 2 weeks after. Participants recorded daily tooth sensitivity. To evaluate the influence of concentration and time on bleaching results (ΔE) the one-way ANOVA with Bonferroni post-hoc test and the Student's t-test were used. **Results:** Group 2 showed the highest value of ΔE (ΔE = 10.59 ± 2.68), followed by Group 4 (ΔE = 8.95 ± 2.32), Group 1 (ΔE = 8.05 ± 3.86), and Group 3 (ΔE = 7.08 ± 1.99). There were differences between Groups 2 and 3 (P= 0.001) and between Groups 2 and 1 (P= 0.032). The same product applied overnight was more effective than applied 1 hour a day (P< 0.05). Different concentrations during the same application time achieved similar results. The reported tooth sensitivity was mild. (*Am J Dent* 2017;30:329-334).

Clinical significance: At-home bleaching is time but not concentration dependent and its secondary effects depend on the active agent concentration; therefore, there is no need to use high concentration products. The most effective protocol is low concentrations (10% carbamide peroxide) with overnight use.

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Introduction

Over the last few decades, treatments to improve esthetic appearance have been on the rise, and consequently, there is a growing demand for tooth bleaching.[1] Nowadays dentist-supervised at-home bleaching for vital teeth is considered an effective, minimally invasive and safe treatment.[2-4]

The active agent of the majority of at-home bleaching systems is carbamide peroxide (CP) or hydrogen peroxide (HP).[1,4,5] CP is a precursor of HP, which upon contact with water breaks down to HP and urea,[4,5] which means that a gel of 10% CP is roughly equivalent to one of 3% HP.[6] The American Dental Association (ADA) recommends using 10% CP, because it is the most studied concentration.[7] However, different concentrations of HP and CP gels are currently used.[8-10] The gels of CP range between 10 and 22%, and those of HP fall between 3 and 10%.[11] Many randomized trials compared similar or equivalent concentrations of different active agents, but to the best of our knowledge there are no articles comparing the efficacy of unequal concentrations.

At-home bleaching products can be applied during the day or night, depending on the patient's preference.[10,12] Application times for the same concentration of active agents vary between studies, ranging from 30 minutes to 8 hours.[13-18]

Tooth bleaching efficacy can be evaluated using subjective or objective methods.[5] Color guides are useful,[19,20] but they are also subjective.[5,20] Dental colorimeters and spectrophotometers are based on CIE L*a*b* and CIE L*C*h* parameters, and have been widely used to objectively determine the effectiveness of bleaching.[13,14,16,18,21-30] The CIE L*a*b* is a three dimensional color scale system, developed by the International Commission on Illumination (CIE) in 1978.[31] L* indicates the lightness (0 corresponds to black and 100 to white), a* its tendency to green (negative values) or to red (positive values), negative values of b* indicate blue and positive ones yellow. Later, the color space CIE L*C*h* was correlated with the previous one, where L* indicates the lightness and it is the same as in the preceding color space, C* $\left(C^* = \sqrt{(a)^2 + (b)^2}\right)$ represents saturation or chroma (with 0 being no saturation, and 100 the highest saturation or pure color), and h* (h* = $b/\sqrt{(a)^2 + (b)^2}$) the value or hue, indicating the shade or color.[32] Although the CIE recommended a new color difference formula[33] called CIEDE2000, the most commonly used color difference formula in dental research is $\Delta E = \sqrt{(\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2}$.[34,35] The smallest color difference perceivable is approximately 0.5-1.0 ΔE units.[1] The ADA Guidelines for Dentist Dispensed Home-Use Tooth Bleaching Products established that a product is effective when it reaches $\Delta E \geq 4.0$ units, comparing post-treatment scores to pre-treatment scores; the color change must also be toward higher L* and lower b*.[36]

Due to the large amount of products and protocols for tooth bleaching available on the market and evaluated in the literature, it is difficult for clinicians to select the best option.[2,3,37,38] There is evidence that at-home bleaching products are effective; nevertheless the comparison between products is difficult, due to methodological bias.[9]

This randomized clinical trial evaluated the efficacy of two products used for at-home bleaching, 10% CP and 7.5% HP, with different application times, 1 hour a day or overnight. The null hypothesis of the study was that using a higher concentration (7.5% HP) or increasing the application time would not increase the effectiveness of at-home bleaching.

Materials and Methods

Study design and patient selection - 80 volunteers were included in this triple-blind randomized clinical and parallel

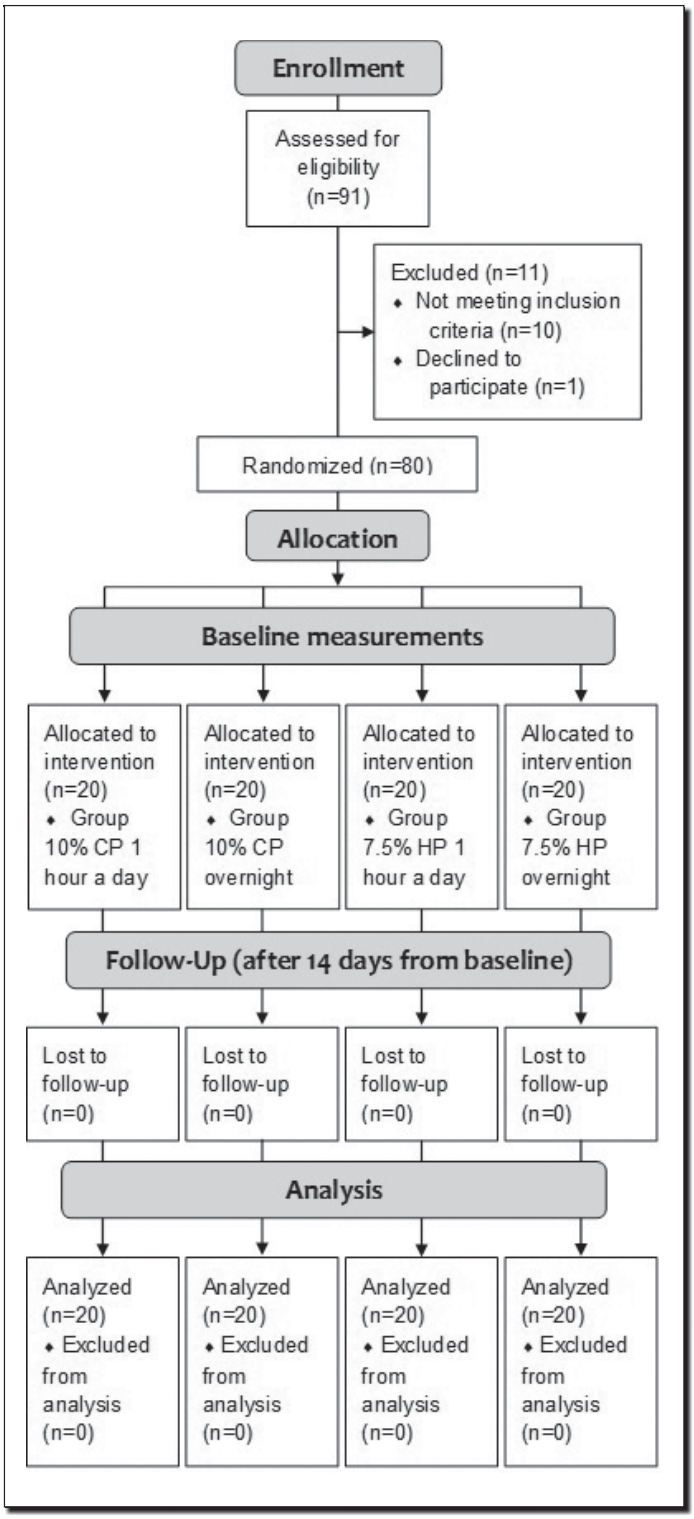

Fig. 1. Consort low diagram.

trial. They were selected from patients who came to the Faculty of Dentistry of the University of Santiago de Compostela, Spain, applying for tooth bleaching. Written informed consent was obtained from each subject. Patients, investigators and the statistician did not know the identification of the groups until the study was finished. The protocol was reviewed and approved by the Ethics Committee of the SERGAS (2015-581), and it was registered at the European Clinical Trials Database (EudraCT) (2016-002896-92). Figure 1 shows the CONSORT flow diagram of the study design and the number of subjects at each phase of the study. The study was developed at the Faculty of Dentistry of the University of Santiago de Compostela, Spain. Volunteers were enrolled after an initial examination by a PhD student (ILD). Participants had to be at least 18 years old, have anterior teeth without any treatment or disease and had good oral hygiene (Sillness and Löe plaque index[39] ≤ 1). Subjects were not included if any of the following criteria were present: periodontal disease, gingival recession, allergy to any component of the product, stains due to tetracyclines or fluorosis and teeth hypersensitivity. Also smokers, pregnant or lactating women and people who had done a prior bleaching treatment were excluded.

Randomization - Subjects were block randomized, with an equal allocation ratio (1:1:1:1), into four groups of 20 individuals according to the active bleaching agent and the application time: 10% CP 1 hour a day, 10% CP overnight, 7.5% HP 1 hour a day, and 7.5% HP overnight. The randomization sequence was generated by an independent statistician using the SPSS[a] 21 software. The list of the allocation sequence was saved and remained inaccessible to the researchers by a person not related to the study.

Material - The bleaching gels used were Perfect Bleach,[b] 10% CP and Pola Day,[c] 7.5% HP.

Experimental procedure - Two weeks before the beginning of the study, all participants received a prophylaxis with calcium carbonate powder (PROHPYflex 3 and PROHPYpearls[d]) to remove extrinsic stains. Alginate impressions (Orthoprint[e]) of both arches were taken to create maxillary and mandibular custom trays. A maxillary custom positioning guide was also prepared to provide a repeatable area for the placement of the spectrophotometer sensor. Trays were fabricated using an Econo-Vac[f] machine and 1 mm soft sheets (Clear-Mouthguard[g]) without reservoirs and were trimmed to 1 mm above the gingival margin. For the positioning guide, 4 mm clear sheets (Clear-Mouthguard) were used. Two orifices were made in the center of the middle third of the right maxillary central incisor and canine, with a 6 mm external diameter trephine, which coincides with the diameter of the spectrophotometer sensor.

At the next appointment (15 days after prophylaxis, Baseline), bleaching trays and positioning guide were tried for accuracy and fit. Subjects received customized trays, application protocol, bleaching agent, and a tooth sensitivity questionnaire. Given that a person not related to the study removed the labels of the bleaching agent and assigned the subjects to the corresponding group at the time of the intervention, subjects and researchers were blinded to the correlation between bleaching products and groups until the study was finished. Furthermore, oral hygiene instructions, toothbrush (GUM Technique Toothbrush[h]) and toothpaste (Colgate Total Toothpaste[i]) were provided to the participants to ensure standardized oral hygiene procedures during the period of the study.

Clinical variables - Clinical variables were measured at baseline and 14 days afterwards.

Color (primary outcome) was measured, at upper right central incisors and canines, objectively with an Easyshade[j] dental spectrophotometer, which records the color detected by the Vita Classical, Vita 3-D Master and shows the CIE L*, a*,

Table 1. Baseline characteristics of the participants per group.

	10% CP 1 hour a day	10% CP overnight	7.5% HP 1 hour a day	7.5% HP overnight
Age (mean ± SD	30.75 ± 10.52	29.29 ± 9.67	31.09 ± 11.17	29.25 ± 9.43
Gender (N & %)				
Male	10 (50%)	11 (55%)	10 (50%)	9 (45%)
Female	10 (50%)	9 (45%)	10 (50%)	11 (55%)
Race	White	White	White	White
CIE parameters (mean ± SD)				
L*	77.98 ± 3.79	79.32 ± 3.46	78.27 ± 4.88	79.22 ± 3.64
a*	-0.56 ± 0.70	-0.15 ± 0.54	0.10 ± 1.09	-0.22 ± 0.60
b*	21.13 ± 4.99	23.68 ± 3.10	22.72 ± 5.46	23.83 ± 5.89
C*	21.15 ± 2.38	23.97 ± 3.02	23.32 ± 2.78	23.98 ± 2.97
h*	92.47 ± 1.78	91.10 ± 2.25	90.60 ± 2.98	91.37 ± 1.87
Tooth sensitivity	None	None	None	None

b*, C* and h* values. Color was measured before the beginning of the treatment (Baseline), and at the end of the treatment (2 weeks from the baseline, Day 14). Before color measurement in each participant, the spectrophotometer was calibrated following the manufacturers' instructions.

The color difference (ΔE) comparing post-treatment scores to pre-treatment scores was established as the primary analysis of the color changes. Secondarily, the differences in CIE L*C*h*a*b* values between the end and the beginning of the study were evaluated.

Participants recorded daily the tooth sensitivity (secondary outcome) through a questionnaire with a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe).[40,41]

Statistical analysis - Continuous variables are expressed as mean ± standard deviation and categorical variables as numbers and percentages. The average of the CIE values was calculated from the data of central incisors and canines. The variable ΔE showed normal distribution (Kolmogorov-Smirnov test), so differences between the four groups were compared with one-way ANOVA with Bonferroni post-hoc test. Variances were assessed with Levene's test, and they were homogeneous. Comparisons in pairs to evaluate the influence of concentration and time on bleaching results (ΔE) between groups were done with Student's t-test for independent variables. The differences in CIE L*C*h*a*b* values between the end (Day 14) and the beginning of the study (baseline) are expressed as ΔL*, ΔC*, Δh*, Δa*, Δb*. Intragroup comparisons of these variables were made with Student's t-test for dependent variables. The differences in ΔL*, ΔC*, Δh*, Δa*, Δb* between groups were also compared with Student's t-test for independent variables. Chi-Square test was used to assess the influence of concentration and time on secondary effects. Also, the power of study was calculated retrospectively using the data of the study (common variance = 9.27, the means of ΔE of the 4 groups and sample size by group = 20) with a significant level of 5%. P values < 0.05 were considered statistically significant. All calculations were performed using the statistical software SPSS 21.

Results

Subjects - All participants, with a mean age of 30.09 (±10.19) years, completed the study (n = 80). The baseline demographic and clinical characteristics of all participants are shown in Table 1.

Bleaching efficacy - In all groups, luminosity (L*) and hue (h*) increased, and chroma (C*), a* and b* decreased (P = 0.000).

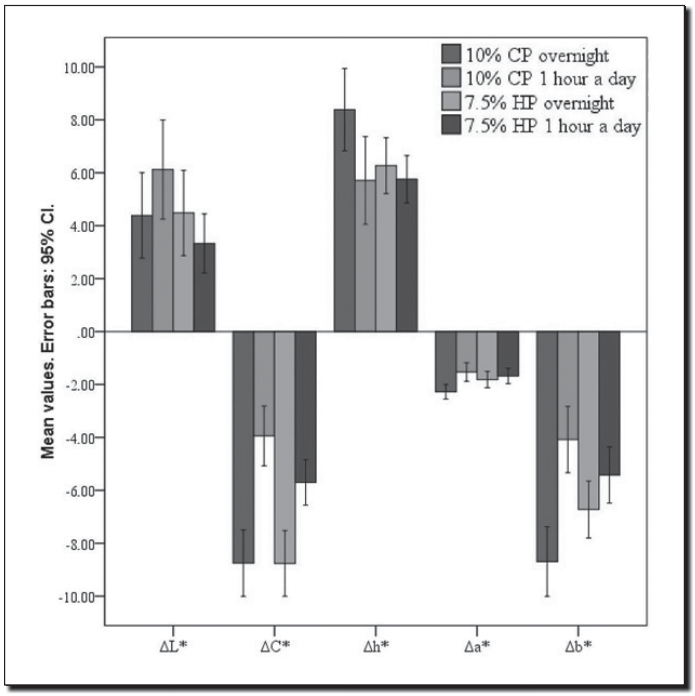

Fig. 2. ΔL*, Δa*, Δb*, ΔC*, Δh* after 2 weeks of treatment.

There were statistically significant differences in CIE L*a*b*C*h* parameters between Day 14 and baseline (P = 0.000). The values of ΔL*, Δa*, Δb*, ΔC* and Δh* for each group are shown in Figure 2. The highest value of ΔE, at the end of treatment, was shown by the 10% CP overnight group (ΔE = 10.59 ± 2.68), followed by 7.5% HP overnight group (ΔE = 8.95 ± 2.32), 10% CP 1 hour a day group (ΔE = 8.05 ± 3.86), and 7.5% HP 1 hour a day group (ΔE = 7.08 ± 1.99). Comparing the four groups together, there were statistically significant differences in ΔE between 10% CP overnight group and 7.5% HP 1 hour a day group (P= 0.001, 95% CI: 1.11-5.92) and between 10% CP overnight group and 10% CP 1 hour a day group (P= 0.032, 95% CI: 0.14-4.95). The power of the study was 88.9%.

Comparison between 1 hour a day and overnight application of the same product - After 2 weeks of treatment, the same product (10% CP and 7.5% HP) applied overnight was more effective (ΔE) than applied 1 hour a day (ΔE = 2.54 ± 1.05, P= 0.021, 95% CI: 0.40-4.68; and ΔE = 1.87 ± 0.68, P= 0.010, 95% CI: 0.48-3.26, respectively). Differences of ΔL*, Δa*, Δb*, ΔC* and Δh* between groups are described in Table 2.

Table 2. Differences in CIE parameters between groups at the end of treatment. CI: confidence interval. SD: standard deviation.

Protocol	Parameter	Differences (mean ± SD)	P	95% CI
10% CP overnight vs 1 hour a day	ΔL*	-1.73 ± 1.81	0.150	-4.13-0.66
	Δa*	-0.75 ± 0.21	0.001	-1.18-0.31
	Δb*	-4.61 ± 0.87	0.000	-6.37-2.85
	ΔC*	-4.81 ± 0.81	0.000	-6.44-3.17
	Δh*	2.67 ± 1.09	0.019	0.47-4.87
7.5% HP overnight vs 1 hour a day	ΔL*	1.15 ± 0.93	0.226	-0.74-3.04
	Δa*	-0.13 ± 0.20	0.510	-0.54-0.27
	Δb*	-1.30 ± 0.72	0.079	-2.76-0.16
	ΔC*	-3.06 ± 0.72	0.000	-4.52-1.60
	Δh*	0.51 ± 0.66	0.445	-0.83-1.85
10% CP 1 hour a day vs 7.5% HP 1 hour a day	ΔL*	2.79 ± 1.04	0.012	0.67-4.92
	Δa*	0.15 ± 0.22	0.488	-0.29-0.59
	Δb*	1.34 ± 0.78	0.096	-0.25-2.93
	ΔC*	1.76 ± 0.90	0.014	0.38-3.13
	Δh*	-0.04 ± 0.90	0.960	-1.88-1.79
10% CP overnight vs 7.5% HP overnight	ΔL*	-0.09 ± 1.09	0.931	-2.30-2.11
	Δa*	-0.46 ± 0.20	0.026	-0.86-0.06
	Δb*	-1.97 ± 0.81	0.020	-3.61-0.32
	ΔC*	0.01 ± 0.84	0.990	-1.70-1.72
	Δh*	2.11 ± 0.90	0.025	0.29-3.94

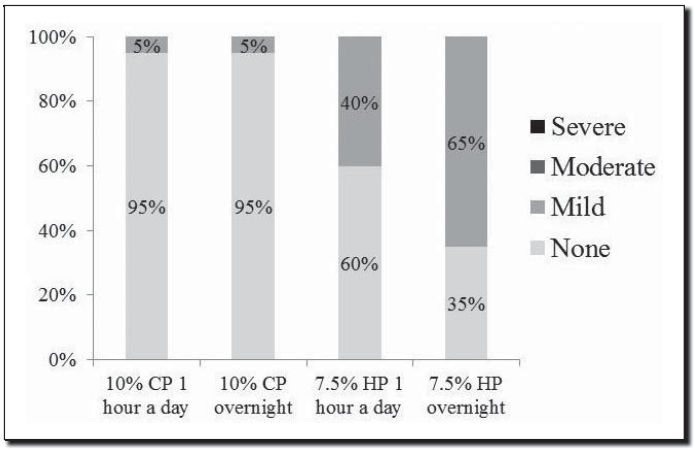

Fig. 3. Incidence of tooth sensitivity reported by participants during the study.

Comparison between different products applied overnight or 1 hour a day - At the end of treatment, no statistically significant differences in ΔE were found between 10% CP and 7.5% HP 1 hour a day (ΔE = 0.97 ± 0.97, P= 0.325, 95% CI: -0.99-2.94), but there were differences between 10% CP and 7.5% HP overnight (ΔE = 1.64 ± 0.79, P= 0.046, 95% CI: 0.34-3.25). Differences of ΔL*, Δa*, Δb*, ΔC* and Δh* between groups are described in Table 2.

Side effects (secondary outcome) - None of the participants reported moderate or severe tooth sensitivity. The incidence of tooth sensitivity reported by the subjects of each group is described in Fig. 3. Applied during the same time (1 hour a day or overnight) 10% CP showed significantly less sensitivity than 7.5% HP (P= 0.020 and P= 0.012, respectively), but no statistically significant differences were found between the different times of application of the same product (P= 0.756 for 10% CP, and P= 0.094 for 7.5% HP).

Discussion

Given the range of at-home bleaching protocols and active agent concentrations available, it is reasonable to compare different concentrations and time applications within the same study, in order to evaluate their efficacy. Nevertheless, in the literature available there are no published articles about this multiple comparison, so it was not possible to calculate the sample size based on a published study. Thus, this research is a pilot study and once it was finished the power was calculated, obtaining a result greater than 80%.

According to the results obtained in this randomized clinical trial, the null hypothesis should be partially rejected because the most effective combination was using low concentrations (10% CP) overnight.

It has been described that bleaching is time and concentration dependent,[4,5,8,10,42] but in fact there are few articles that compare different active agent concentrations or application times. Furthermore, the results of the immediate degree of at-home bleaching are difficult to compare among studies because of the lack of standardization in recording tooth color.[24,42]

Only Cardoso et al[16] compared the efficacy of 10% CP between different application times during a 16-day protocol, using the Vita Easyshade Compact on both central incisors. Similar to the present study, they concluded that, applied for the same length of time, overnight application of 10% CP is more effective than 1-hour application.[16] The present results support the claim that bleaching is time dependent.[12,16] According to studies about in vivo degradation of bleaching gel in trays, this is progressive over time, leaving approximately 40–50% active agent after 1 hour.[43-45] Therefore, the gel applied overnight may not be effective throughout the entire time of application but would be effective for more than 1 hour. Further studies should determine whether applying the bleaching gel for more than 1 hour could be more effective than overnight use.

With regards to the active agent concentration, similar concentrations have usually been compared, obtaining different results. Some studies[29,46] have shown that 15% CP resulted in teeth lighter than 10% CP at a 2-week evaluation, whereas others[13,14,17] have observed that different concentrations are equally effective when applied for the same length of time. However, in the current study unequal concentrations were compared; 7.5% HP equates to more than twice 10% CP, revealing that 10% CP and 7.5% HP rise to a similar color change after 2 weeks of treatment applied during the same time.

Even applied overnight 10% CP is statistically more effective than 7.5% HP. This could be owing to the mechanism of action of the CP, which breaks down to HP and urea, meaning that this dissociation could determine that CP gel has longer efficacy. According to this, Haywood[47] stated that CP gels liberate oxygen more slowly than HP gels. This means that bleaching is not concentration dependent.[13,14]

One limitation of the present study might be that bleaching results were only evaluated immediately after treatment. However, the length of the study was not extended because some studies[25,46] had reported that tooth color is stable after 2 weeks of bleaching.

Tooth sensitivity is the most common side effect of tooth bleaching.[3,4] This effect is transient and disappears at the end of treatment.[17,23] The scales used to subjectively analyze sensitivity range from yes/no,[28,48] 0-3,[40,41] 1–4,[13,16,49] 0–10[21] and 0–20.[10] In addition, a standardized scale should be used to assess tooth sensitivity.

Most participants in previous studies[10,13,16,24,25,44,48,50,51] reported mild sensitivity regardless of the product concentration and time of application, as in this study. The percentage of participants who suffer sensitivity is also variable. Using 10% CP overnight, the percentage ranges from 3–15%,[28] 25%,[48] 72%,[52] to 80%.[16,40] When applying 10% CP for 1 hour a day this percentage varies from 13.33%[16] to 37%.[13] In the present study, in both groups of 10% CP only 5% of participants reported sensitivity. Patients from the groups of 7.5% HP indicated higher intensity of tooth sensitivity than participants from the groups of 10% CP. According to the results obtained in this study and as other authors affirm, the higher the concentration, the greater the sensitivity.[4,10,12,13] On the contrary, other studies[4,16] supported that longer times of application resulted in more sensitivity, although in the current one, it was not significantly influenced by the application time.

In conclusion, the most effective protocol was 10% carbamide peroxide applied overnight. The results of the present randomized clinical trial confirm that at-home bleaching is time but not concentration dependent and the incidence of side effects is influenced by the active agent concentration; therefore there is no need to use higher concentrations (7.5% hydrogen peroxide) for achieving satisfactory bleaching results.

Further studies are required to determine the most effective daily application time for at-home bleaching with low concentration gels (10% carbamide peroxide).

a. SPSS Inc., Chicago, IL, USA.
b. VOCO GmbH, Cuxhaven, Germany.
c. SDI Ltd, Victoria, Australia.
d. Kavo, Biberach, Germany.
e. Zhermack SpA, Badia Polesine, Italy.
f. Buffalo Dental Manufacturing, Syosset, NY, USA.
g. Henry Schein Inc., Melville, NY, USA.
h. Sunstar Americas Inc., Chicago, IL, USA.
i. Colgate Oral Pharmaceuticals, New York, NY, USA.
j. Vita Zahnfabrik, BadSackingen, Germany.

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