In Vitro Study of the Action of Carbamide Peroxide 16% on Human Enamel Study of the Effect of Enamel Color Change Produced By The 16% Carbamide Peroxide Gel Prepared In Compounding Pharmacy

Roberto Paulo Correia de Araujo
Danilo Barral de Araujo
Andreia Nobrega Cavalcanti
Elisangela de Jesus Campos
Maria Thereza Barral Araujo

Abstract

Introduction: in recent years, products containing 16% carbamide peroxide intended for self-application tooth whitening have become widely available in the Brazilian market, independent of prescription or professional supervision. Objective: to evaluate, in vitro, the efficacy of human dental enamel whitening by 16% carbamide peroxide prepared in compounding pharmacy compared to the industrially prepared gel. Methodology: based on experimental protocol conducted in vitro, the 16% carbamide peroxide color change of the human dental enamel was determined, through spectrophotometric measurements based on the CIELab system and conducted after 5, 10, 15 and 20 days of application. Results: The result obtained was applied to analysis of variance and Tukey test. Based on the comparisons, the comprehensive evaluation of parameters ΔE, L, a* and b* demonstrates greater uniformity in the effects produced by the 16% carbamide peroxide of industrial origin compared to the same product prepared in compounding pharmacy. After statistical analysis, the results of this study have proved an effective enamel color change by the carbamide peroxide at 16% concentration, suitable for home use. Conclusion: compounding pharmacy produced carbamide peroxide has a whitening action similar to the one industrially prepared by increasing the brightness and reducing the red and yellow tints of the enamel.*

Keywords: dental enamel; teeth whitening; bleaching agents

Introduction

The home use of 10% and 16% carbamide peroxide over a period of 4 weeks is common. The results of studies with spectrophotometers show that this peroxide in both concentrations promotes tooth whitening, and in the 16% concentration, it is possible to reduce the yellow color in a more intense way. The higher concentrations of whitening agents have been linked to increased longevity of their positive effects, despite the possible emergence of dentinal sensitivity. Even with the consumption of beverages and foods with coloring, the results produced by 10% and 16% carbamide peroxide applied at home for two hours a day for three weeks, show stability of the whitening one year after the treatment.

Studies have been conducted to compare the clinical success and adverse effects of different peroxide concentrations[,7]. In one study, similar whitening action was found between the 10% and 16% carbamide peroxide applied for 8 to 10 hours at night for 14 days. When evaluating safety issues, only gingival irritation was observed. In another study, 20% carbamide peroxide and 7.5% hydrogen peroxide applied at home for one hour twice a day, for two weeks, were compared. The results showed no significant difference between products with regard to gingival or dental sensitivity and whitening efficacy. The reduction in hardness of the enamel can only occur at subclinical levels and not necessarily be the emergence of caries.

The scientific literature often focuses on the decrease of micro hardness, although it recognizes that there is a recovery to baseline values by the contact with post-whitening saliva. There are indicators of changes in micro morphology and micro hardness of the enamel surface after whitening produced by different concentrations of carbamide peroxide and hydrogen peroxide[13]. However, the whitening influence in the morphology and hardness of the enamel surface seems to depend on the concentration of the active ingredients and the presence of minerals such as fluoride and calcium[11].

However, certain studies are controversial regarding the decrease of micro hardness; hence, the recommendation for several successive *in situ* and *in vivo* protocols to be conducted. Micro morphological observations of the enamel treated with 16% carbamide peroxide applied for 8 hours daily, for 14 days, revealed exaggerated prism irregularities, and healthy dentine showed a projection of per tubular areas and intertubular erosion. The micro hardness of a micro hybrid composite resin showed significant decrease due to the effect of five home-use bleaching products with 15% and 16% carbamide peroxide. In recent years, tooth whitening products have become widely available in the Brazilian market for dentist office or home use, prescribed or not by dentists. In addition, whitening products can be found not only in stores that exclusively sell to dentists but also at supermarkets, conventional and compounding pharmacies, where there is free access for the general population, who is unaware of the possible adverse effects of the unsupervised use of whitening agents. Considering the growing demand of the population for dental whitening and the requirement for quicker ways to reach this goal, it is essential to carry out scientifically supported experimental protocols and clinical observations. Thus, the goal of this study is to evaluate, *in vitro*, the efficacy of human dental enamel whitening by the 16% carbamide peroxide gel prepared in compounding pharmacy compared to the industrially prepared gel.

Methodology

Thirty upper and lower human premolars donated by the Tooth Bank of the Teaching and Research Institution of the Metropolitan Union for Education and Culture (União Metropolitana de Educação e Cultura - UNIME) were used in this study. After the removal of residue and soft tissue and teeth cleaning with the aid of Greyce nº 7 curettes and Robinson brushes with pumice and deionized water, the separation of the crowns from the root portion and buccal faces from the lingual or palatine faces with *carborundum* disc on a precision cutter - ELSAW (ElQuip®, São Carlos – SP – Brazil) were performed. Subsequently, the dental sections were included in o-phtalic resin, and the buccal face was kept free on the surface. This procedure ensured the isolation of other areas because they would not be the subject of the trials.

The gel prepared in compounding pharmacy without colorant and neutral pH, contained the 16% carbamide peroxide, sodium pyrophosphate (emulsifier), saccharin sodium (flavoring) and carbopol excipient. Dental bleaching gel carbamide peroxide based on 16% produced by Whitness perfect - FGM, also contains sodium fluoride and potassium nitrate as desensitizing agents. Thus, 30 specimens were created, which were randomly divided into 3 study groups (n=10): Experimental Group 1 (T1) - 16% carbamide peroxide gel, prepared in compounding pharmacy (A Fórmula®, Salvador – BA – Brazil); Experimental Group 2 (T2) - 16% carbamide peroxide gel (Whitness perfect - FGM®, Joinville – SC – Brazil) and a Control Group (C) - with no bleaching treatment and the specimens were daily kept in an oven at 37°C, immersed in remineralizing solution and brushing with white fluoride toothpaste.

The specimens were daily kept in an oven at 37°C, immersed in remineralizing solution. The experimental protocol that was executed for 20 days was based on the following procedures: brushing with white fluoride toothpaste (Oral-B Pró-saúde® 1100 ppm fluoride, Procter & Gamble, Brazil), for 2 minutes, with the aid of Brushing Simulation equipment (ElQuip®, São Carlos – SP – Brazil) adjusted for 540 cycles, simulating the average time of a regular brushing. After the specimens were dried, measurement of the color based on the CIELab system was conducted, through the spectrophotometer VITA Easyshade® Advance (VITA Zahnfabrik H. Rauter GmbH & Co.KG), followed by thermo cycling with the aid of a Thermal Cycling Simulation device (ElQuip®, São Carlos – SP – Brazil), with the application of 100 thermal cycles of 55ºC, 37ºC and 5ºC every 5 seconds, simulating variations in temperature in the oral cavity. Subsequently, 16% carbamide peroxide that was produced in compounding pharmacy and the industrially produced gel were daily applied, for 20 days, while maintaining the specimens in an oven at 37°C, for 4 hours, in a plastic collector container, properly sealed. Once this step was completed, the specimens were washed with deionized water, brushed, and dried again, and then a second color reading was done, to be then kept in remineralizing solution at 37°C until the following day.

This procedure was repeated during the 20-day trial and the spectro photometric readings were performed at the first, fifth, tenth, fifteenth and twentieth day of application of bleaching products. ANOVA was also used to check for differences within a treatment or control group over time (days), along with Tukey test. We used the statistical technique ANOVA for comparing averages for more than two data sets. In this study, we compared two experimental techniques for teeth whitening with a control group to which no technique was employed. It was found in all tested settings, except for those performed on the first day, a statistically significant evidence of difference at the 5% level in the averages of three evaluated groups - control and experiments 1 and 2. The Tukey test applied after the use of ANOVA accounts to check which peer groups differed, since the analysis of variance only detects no equality between the averages of at least one of the groups, not distinguishing which pairs group actually diverge.

Results

Based on the results of the analysis of variance and Tukey test, the data from Tables 1, 2, 3 and 4 shows the comparison of the results from the control and experimental groups 1 and 2, at five different times, after the application of the 16% carbamide peroxide. The evaluation of the degree of whitening obtained is shown after the statistical treatment given to the parameters ΔE, L*, a* and b*.

Table 1: Analysis of variance (ANOVA) to compare the whitening methods, between the Control Group (n = 10), Test Group 1 (n = 10) and Test Group 2 (n = 10). Variable Δ E

Days	Groups			P-value (ANOVA)
	C - Control (n=10)	T1 - Test 1 (n=10)	T2 - Test 2 (n=10)	
	Mean (Standard deviation)	Mean (Standard deviation)	Mean (Standard deviation)	
First day	4,27 (3,50) [a]	5,44 (2,81) [a]	6,24 (3,71) [ab]	0,4291
Fifth day	4,88 (3,42) [a A]	1,82 (1,39) [b B]	4,70 (2,28) [b A]	0,0174
Tenth day	10,08 (3,19) [b A]	4,33 (2,32) [a B]	7,64 (3,18) [a A]	0,0007
Fifteenth day	4,82 (1,90) [a A]	1,95 (0,84) [b B]	3,18 (1,69) [b AB]	0,0013
Twentieth day	6,84 (3,57) [ab A]	3,09 (1,52) [ab B]	9,19 (3,08) [a A]	0,0002
P-value (ANOVA)	0,0009	0,0003	0,0002	

Tukey test: Different lowercase letters imply different values over time (days).
Tukey test: Different Capital letters imply different values between groups (control and treatments 1 and 2).

According to the Tukey test, the control group and the test group 1 were statistically different at all times, as well as between the experimental groups 1 and 2, with the exception of the fifteenth day, in which the two groups did not show a statistically significant difference. The control and test groups 2 diverged at any time. It was found in the control group a statistically significant difference between day one, day 5 and day 15 in relation to the group day 10. In the test group 1 day 1 and day 5 differed from day 15 and the day 5 differed from day 10. In the test group 2 day 5 and day 15 showed a statistically significant difference from group 20, the same occurring between group 10 and 15.

Table 2: Analysis of variance (ANOVA) to compare the whitening methods, between the Control Group (n = 10), Test Group 1 (n = 10) and Test Group 2 (n = 10). VARIABLE L

Days	Groups			P-value (ANOVA)
	C – Control (n=10)	T1 – Test 1 (n=10)	T2 – Test 2 (n=10)	
	Mean (Standard deviation)	Mean (Standard deviation)	Mean (Standard deviation)	
First day	79,41 (5,76)	80,85 (6,95)	83,39 (3,07) [a]	0,2787
Fifth day	79,96 (5,28) [A]	84,12 (7,60) [B]	87,66 (4,45) [ab B]	0,0252
Tenth day	79,56 (6,62) [A]	84,09 (6,50) [B]	90,27 (4,83) [b B]	0,0020
Fifteenth day	80,76 (6,57) [A]	84,31 (6,41) [B]	90,54 (5,04) [b B]	0,0043
Twentieth day	80,82 (4,96) [A]	83,84 (6,20) [A]	90,39 (4,23) [b B]	0,0011
P-valor (ANOVA)	0,9723	0,7596	0,0022	

Tukey Test: Five, ten and fifteen days: C ≠ T1; C ≠ T2; T1 = T2. Twenty days: C = T1; C ≠ T2; T1 ≠ T2.

Tukey test: Different lowercase letters imply different values over time (days).

Tukey test: Different Capital letters imply different values between groups (control and treatments 1 and 2).

It was found in all tested settings, except for that was made on the first day, a statistically significant evidence, at the 5% level of significance of difference in the averages of the three groups, control and tests 1 and 2. According to the Tukey test, except for the twentieth day, the control group and the test group 1 were statistically different at all times. The control group and the test group 2 differed at all times. The test groups 1 and 2 only differed in the twentieth day. In the 10, 15 and 20 days of experiments the test group 2 differs from one test group.

Table 3: Analysis of variance (ANOVA) to compare the whitening methods, between the Control Group (n = 10), Test Group 1 (n = 10) and Test Group 2 (n = 10). Variable a*

Days	Groups			P-valor (ANOVA)
	C – Control (n=10)	T1 – Test 1 (n=10)	T2 – Test 2 (n=10)	
	Mean (Standard deviation)	Mean (Standard deviation)	Mean (Standard deviation)	
First day	-0,12 (1,91)	-0,74 (1,13) [a]	0,01 (1,89)	0,5741
Fifth day	2,13 (2,47) [A]	-0,89 (1,25) [a B]	-0,16 (1,46) [B]	0,0024
Tenth day	2,22 (2,01) [A]	-1,50 (1,06) [ab B]	-1,11 (1,36) [B]	<0,0001
Fifteenth day	2,32 (2,08) [A]	-1,71 (1,15) [ab B]	-1,33 (1,19) [B]	<0,0001
Twentieth day	0,76 (1,90) [A]	-2,49 (1,02) [b B]	-1,69 (1,05) [B]	<0,0001
P-valor (ANOVA)	0,0500	0,0085	0,0500	

Tukey Test: Five, ten, Fifteen, and twenty days: C ≠ T1; C ≠ T2; T1 ≠ T2.

Tukey test: Different lowercase letters imply different values over time (days).

Tukey test: Different Capital letters imply different values between groups (control and treatments 1 and 2).

It was found in all tested settings, except for that, one performed on day 1, that there is a statistically significant difference at the 5% level of significance in the averages of the three groups, control, and tests 1 and 2. According to the Tukey test, the control group and the test group 1 were statistically different at all times, the same occurring with the control and test group 2. The test groups 1 and 2 did not diverge at all. In the test group, 1 after the first and fifth day there was a difference from the twentieth day.

Table 4: Analysis of variance (ANOVA) to compare the whitening methods, between the Control Group (n = 10), Test Group 1 (n = 10) and Test Group 2 (n = 10). Variable b*

Dias	Groups			P-valor (ANOVA)
	C – Control (n=10)	T1 – Test 1 (n=10)	T2 – Test 2 (n=10)	
	Mean (Standard deviation)	Mean (Standard deviation)	Mean (Standard deviation)	
First day	29,65 (6,36)	27,16 (4,02) [a]	30,61 (8,48)	0,4866
Fifth day	35,97 (7,32) [A]	25,94 (2,99) [a B]	30,64 (6,50) [AB]	0,0031
Tenth day	36,37 (5,25) [A]	22,36 (2,58) [b B]	27,85 (6,06) [C]	<0,0001
Fifteenth day	36,46 (5,22) [A]	20,45 (2,21) [b B]	26,31 (5,98) [C]	<0,0001
Twentieth day	33,48 (6,24) [A]	18,84 (2,54) [b B]	25,24 (6,51) [C]	<0,0001
P-valor (ANOVA)	0,0772	<0,0000	0,2768	

Tukey Test: Five days: C ≠ T1; C = T2; T1 = T2. Ten, fifteen and twenty days: C ≠ T1; C ≠ T2; T ≠ T2.

Tukey test: Different lowercase letters imply different values over time (days).

Tukey test: Different Capital letters imply different values between groups (control and treatments 1 and 2).

It was found in all tested settings, except for that was made on the first day, there are statistically significant evidence, at the 5% level of significance of difference in the averages of three groups, control and tests 1 and 2. Control and test groups first diverged at all times. Control group and test 2 diverged to ten, fifteen, and twenty days, the same checking the test groups 1 and 2. In the test group 1, both the first and the fifth day differed from day ten, fifteen-twenty.

Discussion

Mouthwashes, toothpastes, gels and self-applied tapes containing bleaching agents have shown favorable effects on dental aesthetics. However, possible adverse effects should be considered, among which transdentinal cytotoxicity[15]. The performance of bleaching procedures conducted by individuals has been common in Brazil due to the free commerce of these products, regardless of professional prescription and guidance. In the case of a research conducted *in vitro*, the concern was to investigate the whitening potential of two home-use products, an industrially produced one, and a second one prepared in compounding pharmacy.

Therefore, the CIELab system[16] was opted for because it is a method that allows a three-dimensional analysis of color based on three axes: L* – the parameter that measures the degree of enamel brightness; a* – the parameter that translates the variation in the red-green axis and b* – the parameter that shows the variation in the yellow-blue axis. These parameters ensure the determination of the color difference at two different times, by finding the variable ΔE. The results of this study shows that there was effective bleaching of samples with the use of 16% carbamide peroxide in both gels. It can be said that the other components of the two products did not have any interference from the bleaching of the specimens. These findings are consistent with the scientific literature that records the bleaching action of this chemical agent, although it notes that the highest concentrations are responsible for the appearance of dentinal sensitivity[1, 2, 5].

It is worth noting that the tooth whitening was only possible due to the permeability of the tooth structure to the chemical bleaching agent that had the ability to freely diffuse through the enamel and dentin, acting in the organic portion of these structures and therefore promoting whitening. With the spectrophotometric reading results that express the measurement of color intensity of the specimens, it was found that in all tested configurations, with the exception of the one done on the first day, there is statistically significant evidence at 5% significance level, of difference in the means of the three evaluated groups, C, T1 and T2 (Table 1). The results obtained and statistically treated reaffirm the bleaching power of the 16% carbamide peroxide, which is consistent with several studies that identify in this concentration the action of the chemical product in the gel form, indicated for home-use application under professional supervision, despite the record of similar action produced by this bleaching agent in the 10% concentration.

However, one cannot exclude the possibility that there is influence of the whitening on the morphology and micro hardness of the enamel surface depending on the increasing concentrations of the carbamide peroxide, hence the importance of conducting protocols and technological resources that evaluate the influence on the morphology of the treated enamel. After applying the Tukey test to the values assigned to ΔE, the control group and the experimental 1 group showed a statistically significant difference at all times, and the same happened between the T1 and T2 groups, except for the fifteenth day, in which the two test groups did not show statistically significant difference (Table 1). These results indicate the positive action of the carbamide peroxide in the specimens that made up the test groups.

Regarding the variable L*, which is quantified on a scale ranging from 0 (black) to 100 (white)[16], once the results assigned to the control group were compared to test groups 1 and 2, significant differences were found after 5, 10, 15 and 20 days of application of the bleaching products. It is worth noting that a significant difference was only found between the experimental groups after 20 days of treatment, therefore indicating similar whitening between the industrial origin product and the one prepared in compounding pharmacy. In all configurations tested, with the exception of the one performed on the first day, it is found that there is statistically significant evidence for parameter L*, at the 5% difference level in the means of the three evaluated groups, C and test 1 and 2 (Table 2). According to the Tukey test, with the exception of the twentieth day, the group C and group T1 showed statistically significant difference at all times. The control and T2 groups diverged at all times, but T1 and T2 groups only diverged on the twentieth day. Therefore, it can be assumed that despite the experimental groups showing similar action, the greatest effect on enamel brightness is credited to the industrial product.

Parameter a*, whose color variation is between -80 and +80, i.e., in the red-green axis, revealed statistically significant evidence at the 5% significance level, in all configurations tested, with the exception of the one done on the first day, of difference in the means of the three evaluated groups, C and T1 and T2 (Table 3). After the Tukey test was applied, the control group and the test 1 group showed statistically significant difference at all times, and the same was verified with the C and experimental T2 groups. Test groups 1 and 2 did not diverge at any time, therefore variable a* was found to have equal influence on the whitening between the test groups, regardless of the product.

As to parameter b*, whose color variation is also between -80 and +80, therefore in the yellow-blue axis, it started showing a difference between the control group and the experimental ones, and also among the latter, after 5 days, thus showing differences considered statistically significant, at 5%. Therefore, the variable b* also had the same influence on whitening, regardless of the used product (Table 4).

Therefore, after the first applications of 16% carbamide peroxide, there was an increase in brightness (parameter L*) and elimination of the red color, however, some pigmentation with a tendency to green remained (parameter a*). With the continued application of the gels, a more pronounced enamel brightness was obtained (parameter L*) and a sharp decrease of the yellow color pigmentation (parameter b*). Regarding the ΔE units attributed to the original enamel samples and the dental structure treated with bleaching products, numerical values of clear visual perception were achieved.

Based on the comparisons, the comprehensive evaluation of parameters ΔE, L*, a* and b* demonstrates greater uniformity in the effects produced by the 16% carbamide peroxide of industrial origin compared to the same product prepared in compounding pharmacy. Finally, one cannot lose sight that in recent years in Brazil, products destined for tooth whitening have become widely available in the Brazilian market for use in dentist office or at home, prescribed by dentists or not, despite the report of possible adverse effects, among which transdentinal cytotoxicity. This understanding justifies the importance of professional supervision for guidance of clinical procedures, as well as the origin of bleaching products aimed at their rigorous quality control to prevent abusive use by the population.

Conclusion

Based on the results obtained, it can be concluded that 16% carbamide peroxide of prepared in compounding pharmacy and industrial origin produce are efficient at bleaching the dental enamel, according to the ΔE values. It is further concluded that the bleaching action of the tested products was due to the increase in brightness and the decrease in red and yellow tints, also considering the possibility that more uniform bleaching results are obtained with the manufactured products. The dissemination of these results certainly will contribute to the professional information, clarification, and guidance that can be given to patients who need this treatment.

According to Zanin et al., which professionals and patients need to know is that any aesthetic treatment, besides advantages also has some limitations and these are not just the selected techniques, but primarily in the expertise of each tooth limit (structure formation and pathological physiological effects).

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