

Intradermal irritation of dental bleaching agents in rats

Carla Elisa Borin GONÇALVES¹ (CNPq-fellowship), Ligiane Vieira TOKANO-RAMOS¹ (CNPq-fellowship), Renata Correa PASCCOTO (Departamento de Odontologia, Universidade Estadual de Maringá); Ciomar Aparecida BERSANI-AMADO² (Departamento de Farmácia e Farmacologia, Universidade Estadual de Maringá, Avenida Colombo, 5790-CEP 87020-900, Maringá, PR, Brazil)

KEY WORDS tooth bleaching; urea; hydrogen peroxide; irritants; intradermal injections; Evans blue

AIM: To evaluate the irritative potential of three dental bleaching agents (hydrogen oxide, carbopol, and carbamide peroxide). **METHODS:** In rats, Evans blue (2.5 %, 1 mL·L⁻¹) was injected iv and later each test solution was injected intradermally on the back. After the concentration of the dye in the stained skin area was determined by spectrophotometric analysis. **RESULTS:** All the dental bleaching agents caused increase of vascular permeability and the intensity varied with the time. **CONCLUSION:** Dental bleach agents had a great potential for irritating soft tissues.

Since the home technique for whitening living teeth was described^[1], a wide variety of solutions has been introduced^[2,3]. Home dental bleaching agents differed from conventional bleaching agents in their mode of application as well as the chemical agent used^[2,3]. The original technique consist of self-application of a product based on carbamide peroxide (10 % to 15 %) or hydrogen peroxide (1 % to 10 %), which was kept in contact with the teeth by means of a plastic or acrylic resin mold for 2 - 8 h daily for 4 - 6 wk. The polymer carboxypolymethylene (carbopol) is a constituent of some commercial products with a carbamide peroxide base. Carbopol acts as a thickener, aiding adherence to the tissues^[2,3].

The effectiveness of dental bleaching agents is well established^[4]. However, the effects of these products on the soft tissues and teeth are

not well understood, nor are their systemic effects when utilized for prolonged periods^[4-6].

The acid nature of carbamide peroxide can cause undesirable transitory effects in some patients such as soft tissue irritation, gastric irritation, and sore throats, in addition to altering the normal mouth flora, causing hypertrophy of the lingual papillae, and even possibly potentializing the carcinogenic effect of some substances^[6,7]. These effects occurred because of the peroxide ion coming into close contact with the alveolar mucosa and the possibility of the patient ingesting the material. Because of these side effects, the effects of home dental bleaching agents after prolonged or excessive use, unsupervised by the professional dentist, are called into question. The objective of present study was to evaluate the irritative potential of substances used as home dental bleaching agents.

MATERIALS AND METHODS

Rats Ninety Wistar rats (♂, weighing 200 - 250 g) were used.

Vital stain exudation technique The vital stain exudation technique that characterized the increase of vascular permeability induced by certain substances was carried out according to the methods^[8]. Rats anesthetized by inhaling ethyl ether, were injected iv through the dorsal penile vein with a 2.5 % solution of Evans blue, 1.0 mL·kg⁻¹. After depilation and antiseptis of the back, 0.1 mL of each test solution (10 % hydrogen peroxide, 10 % carbamide peroxide with or without 1 % carbopol) was injected id on the back at different sites. As a control, 0.1 mL of saline was injected. A system of rotation of application sites was used during inoculation of the solutions. After 0.5, 1.5, 3, 6, and 24 h, the rats were killed by exsanguination, their dorsal skin was excised, and the sites showing a halo of blue edema were cut out. The pieces of skin were reduced to fragments, immersed in 5 mL concentrated

¹ Supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico-Programa de Bolsa de Iniciação Científica (CNPq-PIBIC/95-6).

² Correspondence to Dra Ciomar Aparecida BERSANI-AMADO, Phn 86-44-261-4040, Fax 86-44-263-5116.

Received 1997-09-17

Accepted 1998-06-25

formamide, and maintained at ambient temperatures (25 °C) for 48 h to extract the dye. The resulting solutions were filtered through glass wool. The concentration of dye was determined by spectrophotometric analysis at $\lambda = 620$ nm. For comparative purpose one group of animals was injected with 0.05 mL of each test solution and the rats were sacrificed after 3 h.

Statistical analysis Statistical analysis of the data was performed by ANOVA. Significant data were submitted to Duncan's test. Student's *t*-test was used to compare 2 independent means. The 5 % significance limit was used.

RESULTS

All the solutions caused increases in exudation of Evans blue stain. The intensity varied according to the solution injected, and with the time following the injection. Solutions of 10 % hydrogen peroxide and 10 % carbamide peroxide without carbopol induced greater exudations during the first hour after injection, reaching a peak effect at 3 h. The exudation induced by the 10 % carbamide peroxide together with carbopol, though less intense during the first hour, reached a peak of the same intensity (Fig 1).

Smaller volumes (0.05 mL) of the respective solutions still caused increases in exudation 3 h following injection, compared to the control and to 1 % carbopol. Therefore,

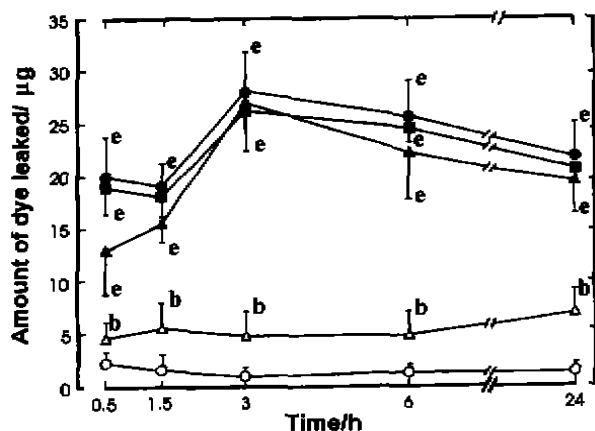


Fig 1. Dye leakage after id injections (0.1 mL) of saline (○); carbopol (Δ); 10 % hydrogen peroxide (●); 10 % carbamide peroxide with 1 % carbopol (▲) and without carbopol (■) previously given Evans blue 25 $\mu\text{g} \cdot \text{kg}^{-1}$. $n = 8 - 13$ rats, $\bar{x} \pm s$. ^b $P < 0.05$ vs control. ^e $P < 0.05$ vs carbopol and control.

the intensity of effect of these agents on vascular permeability appeared to be related to the volume administered (Tab 1).

Tab 1. Amount of dye leaked (μg) after id injections of 0.1 or 0.05 mL of carbopol (C); 10 % hydrogen peroxide (PH); 10 % carbamide peroxide with 1 % carbopol (PCC) and without carbopol (PC). $\bar{x} \pm s$. (n) = number of rats. ^a $P > 0.05$, ^b $P < 0.05$ vs 0.1 mL.

	Dose/mL	
	0.1 (n)	0.05 (n)
PH	26.8 \pm 4.0 (11)	12.5 \pm 4.1 (8) ^b
PC	25.5 \pm 4.2 (11)	13.0 \pm 4.5 (8) ^b
PCC	25.8 \pm 3.5 (12)	11.5 \pm 4.0 (8) ^b
C	3.2 \pm 1.9 (8)	1.9 \pm 0.9 (8) ^a

DISCUSSION

Home dental bleaching agents, also known as "Nightguard Vital Bleaching", are widely used, mainly because of their ease of application, low cost, and high success rate. These agents, consisting mainly of carbamide peroxide and carbopol, are water soluble and unstable, dissociating into hydrogen peroxide and urea upon exposure to saliva^[9].

There are few published studies on the effects of the constituents of home bleaching agents on the tissues, and even these are highly controversial. On the other hand, there are innumerable reports of the effects of hydrogen peroxide on the tissues. These effects include gingival inflammation and lesions of the mucous membranes, in addition to damage to periodontal tissues, dental pulp, pulp enzymes, and severe edema of the tongue. Moreover, there are indications that chronic use of hydrogen peroxide may alter the normal mouth flora and consequently cause hypertrophy of the lingual papillae and infection of the mouth by opportunistic microorganisms^[10-12].

According to some studies, the 10 % carbamide peroxide solution, which is equivalent to 3 % of the (30 % - 35 %) solution of hydrogen peroxide used in the conventional dental bleaching technique, is effective and apparently safe. Harmful effects occur only in conditions when the application time and dosage of peroxide used in the home bleaching technique are exceeded^[3]. There are reports that the toxicity

and mutagenicity of hydrogen peroxide is dose-related, and that the concentration used in the home bleaching technique is not sufficiently strong to damage soft tissues^[4].

However, other studies have indicated a concern with the use of dental bleaching agents, which can cause sensitivity of the teeth, gingival irritation, soft tissue lesions, and cytotoxicity, in addition to potentializing the effect of some carcinogens^[12-15].

The results of the present investigation demonstrated that 10 % carbamide peroxide, associated or not with carbopol, caused an increase in exudation of Evans blue stain, indicating an irritative effect on the living tissues. This effect intensified with greater volumes of solution injected. Additionally, it was observed that carbamide peroxide with carbopol initially retarded exudation of the stain compared to carbamide peroxide without carbopol. This is in accordance with the observations^[3] that solutions that liberate oxygen rapidly (ie, without carbopol) free a maximum amount of oxygen in less than 1 h, while solutions that liberate oxygen slowly (ie, with carbopol) require 2 - 3 h for total liberation of the oxygen. Therefore, the participation of H₂O₂ hydrogen peroxide in the local irritative process of these agents is suggested.

These data are in accordance with the studies of Gage *et al*^[13], who made local applications of 10 % carbamide peroxide or 3 % hydrogen peroxide to the gingiva of dogs for 8 h, and observed that both products caused lesions of the soft tissues. They suggested that the toxic effect of the bleaching agents was probably caused by the H₂O₂ component of the carbamide peroxide, and/or its products.

Considering that the effect of home dental bleaching agents began after 2 - 3 wk of use^[2], that the treatment period might vary considerably^[3], and that the application of home dental bleaching agents was effected by the individual. It was possible that unknown quantities of these agents might be used and ingested during the procedure, or even accidentally consumed by children. Therefore, the results of this study suggest that the use of home dental bleaching agents be rigorously

monitored. Their use without due caution may create conditions in which the bleaching agents, in close contact with living tissues, may cause the appearance of lesions.

ACKNOWLEDGMENTS To Mr Jailson Araujo DANTAS for his technical assistance.

REFERENCES

- 1 Haywood VB. Nightguard vital bleaching letter. *Quint Int* 1989; 20: 697.
- 2 Christensen GJ. Tooth bleaching, home-use products. *Clin Res Assoc News Letter* 1989; 13: 1-3.
- 3 Haywood VB, Heymann HO. Nightguard vital bleaching: how safe is it? *Quint Int* 1991; 22: 515-23.
- 4 Haywood VB. History, safety and effectiveness of current bleaching techniques and applications of the nightguard vital bleaching technique. *Quint Int* 1992; 23: 471-88.
- 5 Berry JH. What about whiteners? Safety concerns explored. *J Am Dent Assoc* 1990; 121: 223-5.
- 6 Powell LV, Bales DJ. Tooth bleaching: its effects on oral tissues. *J Am Dent Assoc* 1991; 122: 50-4.
- 7 Haywood VB, Leech T, Heymann HO, Crumpler D, Bruggers K. Nightguard vital bleaching effects on enamel surface texture and diffusion. *Quint Int* 1990; 21: 801-4.
- 8 Udaka K, Takeuchi Y, Movat HZ. Simple method for quantification of enhanced vascular permeability. *Proc Soc Exp Biol Med* 1970; 133: 1384-7.
- 9 Haywood VB, Houck VM, Heymann H. Nightguard vital bleaching: the effect of various solutions on the enamel surface morphology and color. *Quint Int* 1991; 22: 775-82.
- 10 Cvitko E, Swift EJ, Denehy GE. Improved esthetics with a combined bleaching technique: a case report. *Quint Int* 1992; 23: 91-9.
- 11 Cherry DV, Bowers DE Jr, Thomas L, Redmond AF. Acute toxicological effects of injected tooth whiteners in female rats. *J Dent Res* 1993; 72: 1298-303.
- 12 Haywood VB, Leonard RH, Nelson CF, Brunson WD. Effectiveness, side effects and long-term status of nightguard vital bleaching. *J Am Dent Assoc* 1994; 125: 1219-26.
- 13 Gage TW, Frazier LW, Wright JM. Oral soft tissue response to topically applied peroxide tooth whitener. *J Dent Res* 1992; 71: 585.
- 14 Leonard RH, Phillips C, Haywood VB. Predictors for sensitivity and irritation in nightguard vital bleaching. *J Dent Res*, 1996; 75: 379.
- 15 Pieroli DA, Navarro MFI, Coradezzi II, Consolaro A. Evaluation of carcinogenic potential of bleaching agents in DMBA-induction model. *J Dent Res* 1996; 75: 332.

422-424
牙齿漂白剂对大鼠的皮内刺激

Gonc., C.E.; Toka., L.V. R 988.2

Carla Elisa Borin GONÇALVES¹, Ligiane Vieira TOKANO-RAMOS¹, Renata Correa PASCOTO, Ciomar Aparecida BERSANI-AMADO²

关键词 牙齿漂白; 豚; 过氧化氢; 刺激剂; 皮内注射; 伊文思蓝

皮内刺激剂