Anti-inflammatory Steroids in the Prevention of Tooth Sensitivity

NCT02956070

Study Protocol and Statistical Analysis Plan

September 20th, 2017

Materials and Methods

The scientific review committee and the committee for the protection of human participants of the local university (protocol number 1.376.881) approved this clinical investigation. It was registered in the clinical trials.gov registry under the identification number NCT02956070. We performed this study using the protocol that the Consolidated Standards of Reporting Trials (CONSORT) statement established. Based on pre-established criteria, we selected 70 volunteers for this study. The study was performed from February 15, 2016, to July 12, 2016.

Two weeks before the bleaching procedures, each volunteer received a dental prophylaxis with pumice and water in a rubber cup and signed an informed consent form.

Study design: This was a randomized, triple-blinded, parallel-group clinical trial in which the volunteer, operator, and evaluator were blinded to the group assignment. A third researcher, not involved in the evaluation process, was responsible for the administration of the drugs. The study was carried out in the clinics of the School of Dentistry of Fluminense Federal University (Nova Friburgo, RJ, Brazil). Patients were recruited as they seek for treatment in the clinics of Dentistry of both Universities. No advertisement was made for participant recruitment. Patients were recruited in the order in which they reported for the screening session, thus forming a sample of convenience.

Inclusion and exclusion criteria: Volunteers included in this clinical trial were at least 18 years old, had good general and oral health, and did not report any type of TS. The volunteers were required to have 8 caries-free maxillary anterior teeth without restorations, be free of periodontal disease and review and sign the informed consent form. The central incisors had to be shade A1 or darker as judged by comparison with a value-oriented shade guide (VITA Classical, VITA Zahnfabrik). Despite the fact that the color shade A1 is one of the lightest colors measurable using VITA Classical, many volunteers with A1 shade teeth seek dental bleaching, as they are dissatisfied with the color of their teeth.

Two calibrated investigators (SM and CG) independently performed the color evaluations with the shade guide. The 2 examiners, blinded to the allocation assignment, schedule the volunteers for bleaching and evaluated their teeth against the shade guide at baseline and 1 week after the procedure. The 2 examiners were required to have an agreement of at least 85% (Kappa statistic test) before beginning the study evaluation.

Volunteers with anterior restorations or dental prostheses, with anterior orthodontic apparatuses or with severe internal tooth discoloration (tetracycline stains, fluorosis, pulpless teeth) were not included in the study. In addition, pregnant and lactating women, participants with any other pathology that could cause sensitivity (such as gingival recession, dentinal exposure, visible cracks in teeth), those taking anti-inflammatory or analgesic drugs, those who smoked or volunteers who had undergone tooth-whitening procedures were excluded. Those who reported past or present health problems in the stomach, heart, kidneys or liver; those who reported the continuous use of anti-

inflammatory or analgesic drugs; those patients with diabetes, hypertension or the use of antihypertensive drugs; or patients who reported allergies to dexamethasone and lactose were also excluded from the study.

Sample size calculation: The primary outcome of this study was the absolute risk of TS. The absolute risk of TS (that is, the number of patients [percent] who reported pain at some point during dental bleaching) was reported to be approximately 90% for a similar 35% hydrogen peroxide bleaching product [20,21,36]. Thus, a minimum sample size of 70 participants was required to have a 90% chance of detecting, as significant at the 2-sided 5% level, a decrease in the primary outcome measure from 90% in the control group to 60% in the experimental group.

Random sequence generation and allocation concealment: The authors used blocked randomization (block sizes of 2 and 4) with an equal allocation ration, using a 3rd-party service (Sealed Envelope), which did not intervene in the study. Opaque and sealed envelopes containing the identification of the groups were prepared.

Study intervention: We divided volunteers into the dexamethasone group, who received the anti-inflammatory (dexamethasone, capsule – 8 mg) and application of a placebo gel, and the control group, who received placebo capsules and the application of desensitizing gel containing 6% potassium nitrate and 0.10% fluoride sodium (Soothe, SDI, Victoria, Australia). All volunteers received the same bleaching treatment, which 4 experienced operators (LP, FC, WA, ED) performed. One week before the in-office bleaching session, volunteers received individual pots containing 6 capsules in total, with the dexamethasone (Handled by Bem Viver laboratory Ltda), or placebo, in identical capsules depending on their allocation group, which contained the same components of the dexamethasone drug except for the active ingredient (Table 1).

The control group received placebo capsules and the application of desensitizing gel containing 6% potassium nitrate and 0.10% fluoride sodium, and the dexamethasone group received the anti-inflammatory (dexamethasone, capsule - 8mg) and application of a placebo gel. Volunteers were treated in 2 clinical sessions with an interval of 7 days (one week) between them. The protocol for use of the product was as follows: The volunteers in the experimental group received 6 capsules of dexamethasone 8 mg each, which was administered orally, initially 2 days before the 1st bleaching query (8mg, 9 AM, 2 days before the bleaching session; 8mg, 9 AM, 1 day before the bleaching session; 8mg, 9 AM, on the day of the bleaching session) [40]. This same scheme was performed for the 2nd bleaching session, which was 7 days after the 1st. The operators instructed the volunteers to increase adherence to the protocol, and the researches made telephone calls and sent cell phone text messages to remind the volunteers of every capsule to be taken.

Before the dental bleaching, gingival tissue was isolated from teeth using a light-cured resin (Gingival Barrier, SDI), and each tooth was light-cured for 10 seconds using a light curing unit with 1200 mW/cm2 light intensity (Radii-cal, SDI). After the placement of a lip retractor (OptraGate – Ivoclar Vivadent), the operator used the 37.5% hydrogen peroxide gel (polaoffice+, SDI) in three 8-

minute applications for both groups in accordance with the manufacturer's directions. The bleaching agent was refreshed every 8 minutes during the 24-minute application period. At the end of each session, a single researcher responsible for the blinding (MB) delivered a single syringe to the operator, which would contain desensitizing gel if the patient was in the control group, or placebo gel containing only carbopol (no active ingredient) if the patient was in the dexamethasone group. The gel was applied with a brush on the labial surface of the whitened teeth for 2 to 3 minutes as the manufacturer (Soothe SDI Dental Limited) directed. Two bleaching sessions were performed 1 week apart.

TS evaluation: TS was evaluated during bleaching and up to 1 hour, 24 hours and 48 hours postbleaching. The volunteer was asked to indicate the numeric value of the degree of sensitivity for each of the periods above, using a 5-point numeric rating scale (NRS) in which 0= none, 1= mild, 2= moderate, 3= considerable and 4= severe [2,4,5,7,23].

In addition, the volunteers were also instructed to record the pain intensity using the visual analogic scale (VAS) [3,6-9]. This scale is a 100-milimeter horizontal line with scores of 0 and 100 at their ends, in which 0 = no sensitivity and 100 = severe sensitivity. The volunteer had to mark with a vertical line across the horizontal line of the scale the intensity of the TS. Then, the distance in millimeters from the zero ends was measured with the aid of a millimeter ruler.

The data from each bleaching session were evaluated separately and were merged. For this purpose, the worst score or numeric value obtained in both bleaching sessions was considered for statistical purposes and the determination of the overall risk and intensity of TS.

If the volunteer scored 0 (no sensitivity) in all time assessments from both bleaching sessions, this volunteer was considered to be insensitive to the bleaching protocol. In all other circumstances, the volunteers were considered to have sensitivity stemming from the bleaching procedure. This dichotomization allowed us to calculate the absolute risk of TS, which represented the percentage of volunteers who reported TS at least once during treatment. We also calculated the overall TS intensity.

Color evaluation: Shade evaluation was performed before 1 week after the 1st bleaching session, but before the 2nd session, and 1 week after the 2nd bleaching session. Color evaluation was not performed immediately after each bleaching session so that the effect of dehydration and demineralization on color measures could be avoided. We performed the color evaluation using the shade guides of VITA Classical and the VITA Bleachedguide 3D-MASTER. (VITA Zahnfabrik).

For the color evaluation, the VITA Classical shade guide's 16 tabs were arranged from highest (B1) to lowest (C4) value. Although this scale is not linear in the truest sense, we treated the changes as representing a continuous and approximately linear ranking for the purpose of analysis, as already performed in several published studies [2,3,5,8,9,15,23,25]. The VITA Bleachedguide 3D-MASTER contains lighter shade tabs and is already organized from the highest (0M1) to lowest (5M3) value [24]. The measurement area of interest for shade matching was the middle 1/3 of the facial surface of the central incisor, according to the American Dental Association guidelines [4,12,15].

The 2 examiners, masked to the allocation assignment, scheduled the volunteers for bleaching and evaluated their teeth against the shade guide at the different time assessments. Color changes were calculated from the beginning of the active phase up to and including recall times by calculating the change in the number of shade guide units (ΔSGU), which occurred toward the lighter end of the value-oriented list of shade tabs. In the event of disagreements between the examiners during shade evaluation, a consensus was reached through discussion.

Statistical analysis

We performed the analysis after the intention-to-treat protocol, and we involved all participants who were randomly assigned [21]. In cases of missing data, the last observation was carried forward. The statistician was masked to the study groups. The absolute risk of TS and its intensity were evaluated by using Fischer's exact test. ($\alpha = 0.05$). The authors calculated the relative risk as the confidence interval for the effect size.

Comparison of the TS intensity (NRS data) of the 2 groups at the 2 different assessment points were performed by using the Mann-Whitney U test, and comparisons between times within each group were performed using the Friedman test. The comparisons of the TS intensity obtained with the VAS scale were evaluated by using a 2-way repeated measures ANOVA and Tukey's test.

Color changes between groups (ΔSGU between base line versus 1 week after the 2nd bleaching session) were compared by using a t test, and the shade changes were evaluated by using Student's t test. In all statistical tests, the significance level was 0.05. We performed all analyses by using the software SPSS for windows version 20.0 (IBM).

Results

We screened 123 participants examined in the dental chair to check if they met the inclusion and exclusion criteria (Figure 1). The bleaching procedures were implemented exactly as planned and no modification was performed.

Characteristics of included participants: The baseline color of the volunteers was similar (control group: 5.9 [1.9]; dexamethasone: 5.6 [2.1]); the mean age (SD) between volunteers was similar between the groups (control: 22.5 [2.1] and dexamethasone: 22.3 [2.7]), ranging from 19 to 29 years. Thirty-four percent of the volunteers from the control group, and 23% of the volunteers from the dexamethasone group were men.

Protocol adherence and dropouts: No discontinuity in both treatment groups was found in the clinical investigation. All volunteers attended the recall visit 1 week postbleaching.

Tooth Sensitivity: Two volunteers, 1 from each group, took an analgesic to alleviate the bleaching-induced TS (Tylenol, Janssen Cilag Farmacêutica) in the period from 5 to 7 hours after the 2nd and last clinical bleachings.

Table 2 shows the number of participants who experienced TS during the bleaching regimen in the control group and dexamethasone group. In this table, it is shown that no significant difference was observed between groups ($p = 0.075$). The relative risk, along with the 95% confidence interval, is also evidence that the use of the experimental drug protocol had no effect on the reduction of TS.

Tables 3 and 4 show that the TS was similar in both groups, at different assessment points, in both sessions, using both pain scales. It is also seen that the bleaching-induced TS did not last longer than 48 hours after the bleaching protocol (Tables 3 and 4).

Color Evaluation: Significant whitening was observed in both groups ($P < .001$). The descriptive data from bleaching obtained after the 1st and 2nd bleaching sessions can be seen in Table 5. At the end of the bleaching protocol, a whitening of approximately 3 shade guide units was detected for both groups.

The results of the subjective shade evaluation (VITA Classical: $P = 0.27$; VITA Bleachedguide 3D-MASTER: $P = 0.68$) matched the hypothesis of equality between the groups after bleaching. The effect size and the confidence interval for the overall mean difference is also shown in Table 5 and is evidence of no statistical difference between groups.

Adverse effects: In this study, no reports of adverse effects by volunteers were received.

TABLE 1

PRODUCT	INGREDIENTS
Pola Office + SDI*	• 37.5% hydrogen peroxide • potassium nitrate
Soothe SDI*	• potassium nitrate 6.0% • fluoride ions 0.10% • water 89.60% • thickener 4.20% • sodium benzoate 0.10%
Dexamethasone capsules**	• dexamethasone base 8mg • starch 50% • lactose monohydrate 35% • dibasic calcium phosphate 14% • magnesium stearate 1%
Placebo capsules**	• starch 50% • lactose monohydrate 35% • dibasic calcium phosphate 14% • magnesium stearate 1%
Placebo gel**	• carbopol

* SDI, Victoria, Australia

** Handled by Bem Viver laboratory Ltda, registration number 09047030/0001-28, located at Santa Rosa street, Icarai- Niteroi, RJ, Brazil. Batch of the product: 189155.

TABLE 2

Participants who experienced tooth sensitivity during the bleaching regimen in the control group and dexamethasone group*				
TREATMENT	**TOOTH SENSITIVITY (Nº. OF PARTICIPANTS)**		**ABSOLUTE RISK**	**RISK RATIO (95% CONFIDENCE INTERVAL)**
	Yes	**No**		
Control	33	2	0.94	0.24 (0.05 – 1.26)
Dexamethasone	28	7	0.80	
* Fischer's exact test (p= 0.075).				

TABLE 3

Medians and interquartile (1 and 3 interquartile) ranges of the tooth sensitivity at different assessment points using the numeric rating scale (NRS).

ASSESSMENT TIMES	First Session			Second Session		
	Control	Dexamethasone	Comparison group	Control	Dexamethasone	Comparison group
During bleaching	0 (0-1)[A]	0 (0-1)[A]	NS†	0 (0-1)[A]	0 (0-1)[A]	NS
Up to 1h after bleaching	0 (0-1)[A]	0 (0-1)[A]	NS	0 (0-1)[A]	1 (0-1)[A]	NS
Up to 24h after bleaching	0 (0-1)[A]	0 (0-1)[A]	NS	0 (0-2)[A]	0 (0-1)[A]	NS
Up to 48h after bleaching	0 (0-0)[B]	0 (0-0)[B]	NS	0 (0-0)[B]	0 (0-0)[B]	NS

* Within each column, significant differences are represented by different uppercase letters.
† NS: No significant difference between groups.

TABLE 4

Means (standard deviations) of the tooth sensitivity intensity at the different assessment points using visual analog scales.*

ASSESSMENT TIMES	First Session			Second Session		
	Control	Dexamethasone	Comparison group	Control	Dexamethasone	Comparison group
During bleaching	8.09 (17.06)^{AB}	7.51 (15.46)^{A}	NS†	14.03 (21.39)^{A}	6.46 (6.34)^{AB}	NS†
Up to 1h after bleaching	11.14 (20.08)^{A}	6.31 (12.78)^{A}	NS	14.31 (20.13)^{A}	7.57 (13.46)^{A}	NS
Up to 24h after bleaching	8.26 (13.48)^{A}	5.06 (9.86)^{A}	NS	16.60 (21.57)^{A}	9.77 (20.55)^{A}	NS
Up to 48h after bleaching	2.91 (9.14)^{B}	0.37 (1.54)^{B}	NS	1.91 (5.46)^{B}	1.14 (4.46)^{B}	NS

* Within each column, significant differences are represented by different uppercase letters.
† NS: No significant difference between groups.

TABLE 5

Means (standard deviations) of the change in shade guide units obtained with the VITAL Classical* and VITA Bleachedguide 3D-Master* at baseline versus each bleaching session and 1 week post-bleaching.					
TIME INTERVAL	**COLOR EVALUATION TOOL**	**GROUPS**		***P* VALUE**	**MEAN DIFFERENCE (95% CONFIDENCE INTERVAL)**
		Control	**Dexamethasone**		
Baseline versus 1st Session	**VITA Classical**	2.14 (1.52)	1.89 (1.37)	0.46	0.35 (-0.43-0.95)
	VITA Bleachedguide	1.91 (0.95)	1.86 (0.97)	0.81	0.06 (-0.40-0.52)
2nd session versus 1st Session	**VITA Classical**	0.74 (1.15)	0.71 (1.49)	0.93	0.03 (-0.61-0.66)
	VITA Bleachedguide	1.29 (0.52)	1.23 (0.69)	0.70	0.06 (-0.23-0.35)
Baseline versus 2nd Session	**VITA Classical**	2.54 (2.39)	2.91 (1.96)	0.48	-0.37 (-1.42-0.67)
	VITA Bleachedguide	3.00 (1.19)	3.2 (1.35)	0.51	-0.20 (-0.81 -0.41)
Baseline versus 1 week after 2nd session	**VITA Classical**	2.77 (1.96)	2.26 (1.87)	0.27	0.51 (-0.40-1.43)
	VITA Bleachedguide	3.20 (1.13)	3.09 (1.17)	0.68	0.11 (-0.44 – 0.66)
*Manufactured by VITA Zahnfabrik.					