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ORIGINAL ARTICLE

Effect of acidity of in-office bleaching gels on tooth sensitivity and whitening: a two-center double-blind randomized clinical trial

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Abstract
Objectives The study aimed to compare the tooth sensitivity (TS) and bleaching efficacy of two hydrogen peroxide gels with different pHs (acid pH [Pola Office, SDI] and the neutral pH [Pola Office+, SDI]) used for in-office bleaching.
Materials and methods Fifty-four patients from Brazil and Chile, with right superior incisor darker than A2, were selected for this double-blind, split-mouth randomized trial. Teeth were bleached in two sessions, with 1-week interval. Each session had three applications of 8 min each, according to the manufacturer's instructions. The color changes were evaluated by subjective (Vita Classical and Vita Bleachedguide) and objective (Easy shade spectrophotometer) methods. Participants recorded TS with 0–10 visual analog scale. Color change in shade guide units (SGU) and ΔE was analyzed by Student's t test ($\alpha = 0.05$). The absolute risk and intensity of TS were evaluated by McNemar's test and Wilcoxon-paired test, respectively ($\alpha = 0.05$).
Results All groups achieved the same level of whitening after 30 days of clinical evaluation. The use of a neutral in-office bleaching gel significantly decreases the absolute risk of TS (28%, 95% CI 18–41) and intensity of TS when compared to the acid bleaching gel (absolute risk of 50%, 95% CI 37–63).
Conclusion The use of a neutral in-office bleaching agent gel produced the same whitening degree than an acid bleaching gel but with reduced risk and intensity of tooth sensitivity.
Clinical significance Clinicians should opt to use in-office bleaching with a neutral gel than an acid product because the former causes a significant lower risk and intensity of tooth sensitivity.

Keywords In-office bleaching · Neutral gel · Acidic gel · Tooth sensitivity · Whitening effectiveness

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Introduction

Bleaching procedures have become the most conservative and popular techniques that are used to solve dental discoloration. Consequently, many authors have focused their studies on determining the best clinical approach that produces the least amount of side effects. Although only a 10% carbamide peroxide product has the American Dental Association's seal of acceptance [1, 2], there are some other commercially available bleaching products (i.e., over-the-counter, at-home, and in-office bleaching) that have yielded successful outcomes [1, 3–6].

In-office bleaching is considered an alternative bleaching modality when patients do not adapt well to the use of a daily bleaching tray. This technique is mainly performed with highly concentrated hydrogen peroxide gels; however, there are many in-office bleaching products in the dental market, which makes their choice quite difficult. They vary slightly in the

active concentration of hydrogen peroxide (HP), which ranges usually from 25% to 40%. Some contain additives such as calcium phosphates and desensitizing agents, and they also vary in their mode of application with most of them requiring product replenishment during the in-office bleaching session. Other important difference is the product pH, as they can be very acidic (pH around 2.0) or very alkaline (pH around 9.0) [7–9].

The great majority of the in-office bleaching gels are delivered in a low pH in a way to increase the product's shelf life [8–10]. The disadvantage of such low pH is that it can promote enamel demineralization [11] and changes in chemical composition, morphology, and mechanical properties of the tooth structure [12–14]. In an effort to reduce this side effect, some manufacturers have released in-office bleaching gels with alkaline and neutral pH [7, 15], which are less aggressive to tooth structure. Additionally, the efficacy of hydrogen peroxide bleaching is directly proportional to the increase of the pH of the bleaching gel [16], which is explained by the fact that the dissociation constant of the HP is about 11.5. In a pH of 9, the dissociation rate of the HP was 2.7 times higher than that in an acidic solution (pH = 4.4) [17].

Recently published clinical studies have hypothesized that in-office bleaching agents with alkaline/neutral pH appear to have lower tooth sensitivity risk [18–20]. However, apart from acidity of the bleaching agents, the bleaching gels used in these studies have many other differences, which highlights the need for further studies using bleaching agents with very similar composition apart from their acidity. Therefore, the aim of this study was to compare the color change, risk, and intensity of tooth sensitivity of two in-office bleaching agents from the same brand with different pHs. The null hypotheses that were tested postulated that (1) differences in pHs of in-office bleaching gels would not result in different rates of risk and intensity of tooth sensitivity (TS) and (2) the differences in pHs of in-office bleaching gels would not result in different degrees of color change.

Material and methods

The Center of Higher Education of Campos Gerais (CESCAGE, protocol 390.941) and the University of Chile (protocol 2013/41) Ethics Committees approved this clinical trial. This study was registered at the Brazilian registry of clinical trials under protocol number REBEC:RBR-3h6n6c. The study took place within the dental clinics of both universities from June 2014 to June 2015.

The experimental design followed the CONSORT statement [21]. Based on preestablished criteria, 54 volunteers from the cities of Ponta Grossa (Paraná, Brazil) and Santiago (Santiago, Chile) were selected for this study. Two weeks before the bleaching procedures, all of the volunteers received a dental screening, a dental prophylaxis with pumice, and water in a rubber cup and signed an informed consent form.

Study design and blinding

This was a randomized, split-mouth, double-blinded clinical trial with an equal allocation rate. Both the patient and the evaluator who assessed color changes were blinded to the group assignment. The study took place in the clinics of the School of Dentistry at the CESCAGE, Paraná (Brazil), and the University of Chile, Santiago (Chile).

Eligibility criteria

The patients who were included in this clinical trial were men and women of any age who were in good general and oral health. These participants were recruited by wall announcements at both universities. The participants were required to have six maxillary and mandibular anterior teeth without caries lesions or restorations. The right superior incisor should be shade A2 or darker, as judged by comparison with a value-oriented shade guide (VITA Classical Shade Guide, Vita Zahnfabrik, Bad Säckingen, Germany). Color A2 is the fifth color in the light to dark value VITA classical shade guide scale so that there are still five shades to allow measurement of color changes with this scale. This minimal color shade was already employed in many other clinical trials [22–27].

Pregnant or lactating women and smokers were not included in this trial. Participants with anterior restorations, bruxism habits, severe internal tooth discoloration (tetracycline stains, fluorosis, pulpless teeth), and recessed or exposed dentine were also excluded. Additionally, participants who took anti-inflammatories, analgesics, or antioxidants were not included in the study.

Sample size calculation

The primary outcome of this study was absolute risk of tooth sensitivity. Fifty-four patients were required to have an 80% chance of detecting a decrease in the primary outcome measure from 63% (average absolute risk of tooth sensitivity [28] in the control group) to 36% in the experimental group ($\alpha = 0.05$). The sample size was calculated on the website www.sealedenvelope.com.

Randomization and allocation concealment

Both arches of participants were randomly divided into two groups according to the in-office bleaching gel to be applied. In all patients, the left hemi-arch received the first bleaching gel revealed by the randomization process (acid gel or neutral gel), while the right hemi-arch received second bleaching gel

(acid gel or neutral gel). A third person that was not involved in the research protocol performed the randomization procedure by using computer-generated tables. We used simple randomization (with an equal allocation ratio (www.sealedenvelope.com). Opaque, sealed, and consecutively numbered envelopes containing the identification of the groups were only opened immediately before the beginning of the bleaching protocol.

Study intervention

The operator was not blinded to the procedure, as both in-office bleaching gels had different commercial presentations. However, the participants and the examiners who evaluated the color changes with the value-oriented shade guides (VITA Classical Shade Guide, Vita Zahnfabrik, and VITA Bleachedguide, Vita Zahnfabrik), as well as the Vita Easyshade (Easyshade, Vident, Brea, CA, USA), were not aware of the allocation of the participants within the study groups.

Bleaching procedure

This study employed the *acid gel* 35% HP Pola Office (SDI, Bayswater, Victoria, Australia) and the *neutral gel* 37.5% HP Pola Office+ (SDI, Bayswater, Victoria, Australia) (Table 1). We isolated the gingival tissue of the teeth to be bleached by using a light-cured resin dam (Gingival Barrier, SDI, Bayswater, Victoria, Australia). In compliance with the manufacturer's directions, we applied the HP gels during three 8-min applications for both groups. The products were refreshed every 8 min during the 24-min application period. We performed two bleaching sessions with a 1-week interval. All of the participants were instructed to brush their teeth regularly (i.e., four times a day) with fluoridated toothpaste without whitening components that was provided by the study investigators.

Color evaluation

The examiners recorded the color prior to the commencement of the study and at periods of 1 week and 30 days after the

Table 1 Products, composition, and application regimens

Products	Composition[b]	Application regimen[b]
Pola Office pH = 2.4–2.6[a]	Liquid = 35% hydrogen peroxide and 65% water Power = 73.26% thickeners, 26.2% catalysts, 0.04%, dye 0.5%, and desensitizing agents (potassium nitrate, unknown concentration)	1. Dry teeth and apply gingival barrier to both arches slightly overlapping enamel and interproximal spaces. 2. Light cure in a fanning motion for 10–20 s until gingival barrier is cured. 3. Open powder pot. Take one Pola Office syringe, firmly attach a tip, and carefully pull back plunger to release pressure. Carefully extrude contents of syringe into the pot. 4. Immediately mix using a brush applicator until gel is homogeneous. 5. Apply a thick layer of gel to all teeth undergoing treatment. 6. Leave gel on for 8 min. 7. Suction off using a surgical aspirator tip. 8. Complete steps 6 and 7 twice times (24 min total). 9. After the last application, suction all the gel off, then wash and apply suction. 10. Remove gingival barrier by lifting it from one end.
Pola Office+ pH = 7.0[a]	Gel = 35% hydrogen peroxide and 65% water and desensitizing agents (potassium nitrate, unknown concentration)	1. Dry teeth and apply gingival barrier to both arches slightly overlapping enamel and interproximal spaces. 2. Light cure in a fanning motion for 10–20 s until gingival barrier is cured. 3. Firmly attach a mixing nozzle to the Pola Office+ syringe away from patient. Dispense a small amount of gel on to a mixing pad until a uniform gel is extruded. 4. Using the nozzle as a guide, directly apply a thin layer of gel to all teeth undergoing treatment. A thin layer will help prevent the gel from running. 5. Leave gel on for 8 min. 6. Suction off using a surgical aspirator tip. 7. Repeat steps 5–6 twice times (24 min total). 8. After the last application, suction all the gel off, then wash and apply suction. 9. Remove gingival barrier by lifting it from one end.

[a] According to Freire et al. [9], Jadad et al. [15], and Basting et al. [18]

[b] According to the manufacturer's indications

bleaching treatment by using subjective (value-oriented shade guides VITA Classical Shade Guide and VITA Bleachedguide, Vita Zahnfabrik, Bad Säckingen, Germany) and objective evaluation tools (Easyshade spectrophotometer, Vident, Brea, CA, USA). The Vita Bleachedguide is originally oriented from lightest to darkest color, while the 16 tabs from the VITA classical shade guide were arranged from whitest to darkest as follows: B1, A1, B2, D2, A2, C1, C2, D4, A3, D3, B3, A3.5, B4, C3, A4, and C4. For both shade guide units, the measurement area of interest for shade matching was the middle one third of the buccal surface of the right superior incisor.

For calibration purposes, five participants whom we did not include in the study sample participated in the training phase in each center. The two examiners, in each center, who were blinded to the allocation assignment, scheduled these patients for bleaching and evaluated their teeth against the shade guide at the baseline at 1 week and again 30 days after the procedure. The two evaluators, in each center, presented superior color matching competency according to the ISO/TR 28642 [29]. This means that they have an agreement of at least 85% (Kappa statistic) before beginning the study evaluation (85% of correctly matched pairs of tabs in shade guides). If disagreements occurred during the evaluation, they needed to reach a consensus before the participant was dismissed.

For the objective evaluation, a dense silicone Speedex (Coltène Whaledent AG, Altstaetten, Switzerland) was used to make a preliminary impression of the maxillary arch of the patients. The impression, which was extended to the upper incisor, served as a standard color measurement guide for the spectrophotometer. A window was created on the labial surface of the silicone guide so that the right superior canine could be evaluated. The window was made by using a metallic device with well-formed borders at a radius of 3 mm. Only one of the operators conducted the assessment on all of the participants by using Vita Easyshade (Easyshade, Vident, Brea, CA, USA) before the procedure and 1 week and 30 days after the bleaching process.

The shade was determined by using following parameters that were detected by the Easyshade device: L^*, a^*, and b^*, in which L^* represents the value from 0 (black) to 100 (white) and a^* and b^* represent the shade, where a^* is the dimension along the red-green axis and b^* is the dimension along the yellow-blue axis. The color comparison before and after the treatment was assessed through the differences (ΔE) that were observed between the two colors. Such differences were calculated with the formula: $\Delta E = [(\Delta L*)^2 + (\Delta a*)^2 + (\Delta b*)^2]^{1/2}$.

TS assessment

The patients recorded their perception of TS during the first and second bleaching sessions according to two pain scales. The participants were instructed to record the pain intensity using the visual analog scale (VAS). This scale is a 10-cm horizontal line with scores of 0 and 10 at their ends, in which 0 = no sensitivity and 10 = severe sensitivity. The patient should 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 participants were asked to indicate their experience of TS in the following time intervals: during the treatment up to 1 h, from 1 h up to 24 h post-bleaching, and from 24 to 48 h post-bleaching. The worst score/numerical value that was obtained in both bleaching sessions was considered for statistical purposes.

If the patient scored zero (no sensitivity) in all time assessments from both bleaching sessions, this patient was considered to be insensitive to the bleaching protocol. In all other circumstances, the patients were considered to have sensitivity to the bleaching procedure. This dichotomization allowed us to calculate the absolute risk of TS, which represented the percentage of patients that reported TS at least once during treatment. We also calculated the overall TS intensity based on the worst score/numerical value that was obtained in both bleaching sessions.

Statistical analysis

Preliminary analyses were performed to check if there was any difference between the two research centers. As the same trend (color change, risk, and intensity of TS) was observed in both centers (Brazilian and Chilean), data were merged into a single statistical analysis.

The analysis followed the intention-to-treat protocol and involved all of the participants who were randomly assigned [21]. The statistician was blinded to the study groups. The absolute risk of tooth sensitivity was considered the primary outcome of the present study, and the groups were compared by using the McNemar's test. The confidence interval for the effect size was calculated.

The TS intensity of the groups was compared at each assessment period with the Wilcoxon test. Comparisons between assessment points (during and post-bleaching), within each group, were performed with the Wilcoxon signed-rank test. The color change was used to determine the efficacy of the bleaching treatment. The color change between the baseline and 30 days were calculated for each group. The groups were compared using the Student t test. In all of the statistical tests, the alpha was preset at 0.05.

Results

A total of 145 participants were examined; 54 participants were selected (34 male and 20 female; Fig. 1). The mean

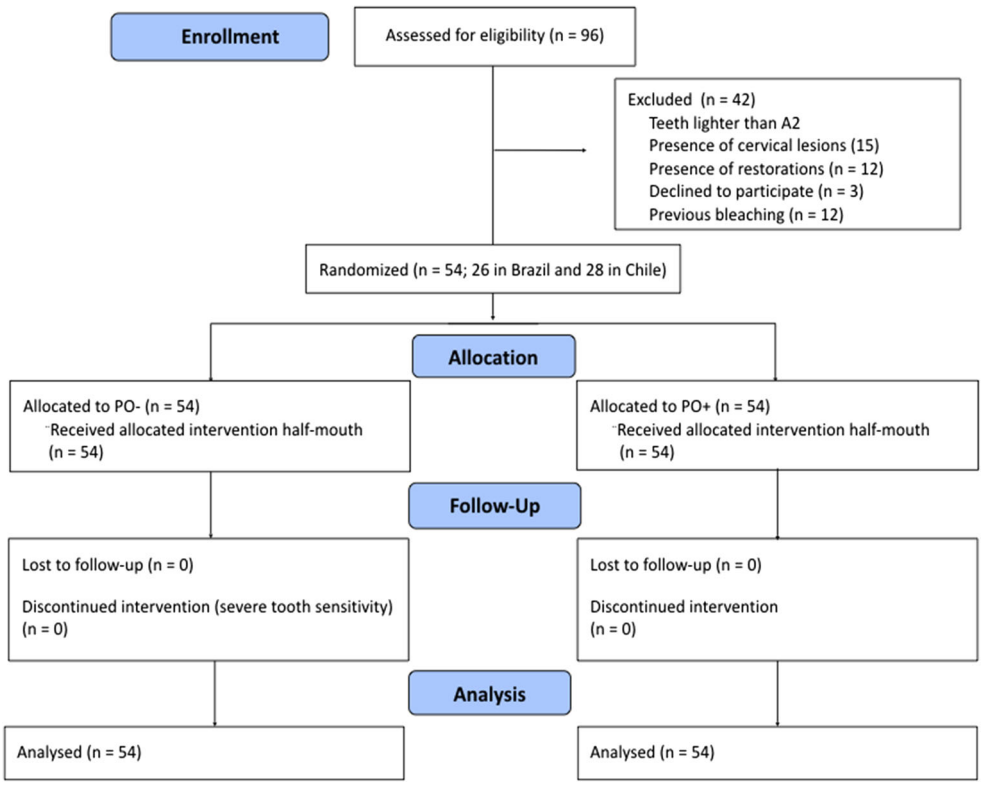

Fig. 1 Flow diagram of study design phases including enrollment and allocation criteria

age (years) of the participants and the baseline SGU are described in Table 2. One can observe comparable data among treatment groups. None of the patients discontinued intervention or presented adverse effects during the intervention. No medication and/or desensitizer was necessary to be prescribed/applied in the participants from this study for the relief of bleaching-induced TS.

Tooth sensitivity

In regard to the absolute risk of bleaching-induced TS, a significant difference was observed between groups as seen in Table 3 (McNemar's test, $p = 0.027$). The risk ratio, along with the 95% confidence interval, is also evidence that the use of the acid gel (Pola Office) produced significant higher risk of bleaching-induced TS than the neutral gel (Pola Office Plus). Similarly, lower intensity of TS was detected for the neutral gel than for the acid gel (Table 4), for both pain scales used in this study mainly in during bleaching ($p = 0.004$). As the results are the same for both scales, only one of them was added.

Color change

Significant whitening was observed in both study groups. A whitening of approximately 5 SGU in the Vita Classical and 3.7 SGU in the VITA Bleachedguide was observed. In terms of ΔE, an average of 8 units was detected for the groups (Table 5). No significant difference between groups was detected under the subjective and objective evaluations (Table 5, $p > 0.06$).

Discussion

The present investigation demonstrated that the pH of the bleaching gel did not have any impact on the degree of whitening produced by the bleaching products evaluated in this study as no significant differences were observed in the degree of color changes between the neutral and acid gel, a finding also observed in earlier clinical trials [18, 20].

Table 2 Baseline characteristics of the participants included in this clinical trial

Characteristics	Acid gel (Pola Office)	Neutral gel (Pola Office+)
Age (mean ± SD, years)	25.2 ± 5.0	22.2 ± 4.0
Baseline color (mean ± SD, SGU VC)	7.5 ± 1.8	7.3 ± 1.4

SGU VC shade guide units Vita Classical

Table 3 Comparison of the number of patients who experienced tooth sensitivity (TS) at least once during the bleaching regimen in both groups along with absolute risk and risk ratio

Treatments	Number of participants with TS		Absolute risk[a] (95% CI)	Risk ratio (95% CI)
	Yes	No		
Acid gel (Pola Office)	27	27	50 (37–63) B	0.57 (0.33–0.92)
Neutral gel (Pola Office+)	15	39	28 (18–41) A	

Risks identified with different capital letters are statistically different

[a] McNemar's test ($p = 0.027$)

Both in-office bleaching gels showed significant whitening after two bleaching sessions. All instruments used for color evaluation showed that both gels were equivalent in terms of color change. A change of approximately five shade guide units in the Vita classical shade guide was observed, which are in agreement with previous studies that performed two in-office bleaching sessions [3, 30, 31].

At first glance, the results of color change herein presented seem to contradict the well-known finding that efficacy of hydrogen peroxide bleaching is directly proportional to the pH of the solution [16]. Indeed, an in vitro study in the dentistry field demonstrated that significant increase occurs in bleaching outcomes at pHs higher than 6, with maximum effectiveness achieved at pH 9.0 when used to bleach wine and tobacco solutions [16]. This best efficacy at alkaline pH is expected since the dissociation constant (pK_a) of the hydrogen peroxide is around 11.5 [17].

In fact, from chemical theories, one knows that, in simplest chemical reactions, the highest concentration of reactants raises collisions per unit time. Hence, the reaction rate increases. However, if the reaction is complex and involves a series of consecutive steps, there might be a limit to which the increased concentration leads to faster reaction rates. We hypothesize that the free radicals produced by the acid 35% hydrogen peroxide already produce enough free radicals to oxidize the organic component of dentin and produce significant whitening. Consequently, the further increases in free radicals that are produced by the neutral gel did not lead to faster bleaching, due to the presence of unknown rate-determining steps in the oxidizing mechanism of tooth bleaching. This might also explain why an earlier clinical trial observed similar degree of whitening when two 15-min application times were used instead of three 15-min applications in each bleaching session [32].

Interestingly, the findings related to the bleaching-induced TS were significantly affected by the pH of the bleaching agents investigated. Bleaching-induced TS is a common side effect that occurs during bleaching treatments [3, 18, 30]. A recent study that evaluated the individual patient data of 11 clinical trials about bleaching revealed that the risk of TS for in-office bleaching was reported to be 62.9% ([95% CI] 56.9–67.3). The risk of TS of the acid gel evaluated in this study was close to average reported in this retrospective of 11 clinical studies. The neutral gel, on the other hand, showed a significant lower risk and intensity of TS than the acid gel, which surprisingly was even lower than what was reported as average for at-home bleaching in this retrospective study [22, 23, 25, 27, 28].

Although very interesting, this finding was already observed in other clinical trials that compared different in-office bleaching agents with different pHs [18, 20]. The same reasons that explain why the neutral gel did not have a higher degree of whitening explain their lower absolute risk and intensity of TS. Stoichiometric experiments showed that the formation of perhydroxyl ion is influenced by pH; thus, the higher is the pH, the more ions are formed, leading to more free radical production [16].

The speed at which perhydroxyl ions are produced is closely related to the pH of the hydrogen peroxide solution. A study

Table 4 Tooth sensitivity intensity (means ± standard deviations) at the different assessment points for both study groups and the statistical comparison

Time assessments	VAS scale	
	Acid gel (Pola Office)	Neutral gel (Pola Office+)
Up to 1 h	1.9 ± 2.1 A	0.9 ± 1.6 B
1 to 24 h	0.2 ± 0.5 C	0.4 ± 0.3 C
24 to 48 h	0.2 ± 0.5 C	0.2 ± 0.4 C

Wilcoxon-paired test ($p = 0.004$). Means identified with the same capital letters are statistically similar

Table 5 Color change in shade guide units (SGU, Vita Classical and Vita Bleachedguide) and ΔE (means ± standard deviations) between baseline and 30 days after bleaching for the two treatment groups

Color evaluation tools	Acid gel (Pola Office)	Neutral gel (Pola Office+)	p value[a]
ΔSGU (Vita Classical)	5.1 ± 1.9	5.2 ± 1.9	0.58
ΔSGU (Vita Bleachedguide 3D)	3.8 ± 1.4	3.6 ± 1.0	0.20
ΔE	8.3 ± 3.5	7.7 ± 3.6	0.06

[a] Student's t test

conducted on bleaching in cotton fabrics using hydrogen peroxide concluded that the rate of hydrogen peroxide decomposition rises significantly with the increase of the pH from 5 to 11 and that such increase reduces the time required for the complete decomposition of the hydrogen peroxide [33]. In this way, it is likely that the faster decomposition of hydrogen peroxide prevents or even minimizes the further travel of HP surplus to the pulp chamber where it may cause pulp damage and induce tooth sensitivity. A further evidence of this hypothesis can be found in the findings of an in vitro study. The authors compared the penetration of HP into the pulp chamber of different in-office bleaching gels and observed that such penetration was much more related to the pH of the bleaching solution than with the concentration of the bleaching product [34].

Further basic studies should be conducted in this field in order to identify the reasons of why the neutral to alkaline gels have lower sensitivity rates than more acid products. Additionally, other clinical products with other product brands are required to allow generalization of these findings to all bleaching brands in the market.

Conclusions

Within the limitations of the present study, in-office bleaching with a neutral gel produced the same whitening degree than an acid product but with a significant lower risk and intensity of tooth sensitivity.

Compliance with ethical standards

Conflict of interest A. Loguercio declares that he has no conflict of interest, F. Servat declares that he has no conflict of interest, R. Stanislawczuk declares that he had no conflict of interest, A. Mena-Serrano declares that she has no conflict of interest, M. Rezende declares that she has no conflict of interest, M. V. Prieto declares that she has no conflict of interest, V. Cereño declares that she has no conflict of interest, M. F. Rojas declares that she has no conflict of interest, K. Ortega declares that she has no conflict of interest, E. Fernández declares that he has no conflict of interest, and A. Reis declares that she has no conflict of interest.

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Ethical approval This clinical study was approved by the Ethics Committee of The Center of Higher Education of Campos Gerais (CESCAGE, protocol 390.941) and the University of Chile (protocol 2013/41) and was conducted according to the Consolidated Standards of Reporting Trials Statement and Helsinki Declaration of 1975 revised in 2000.

Informed consent All persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study were omitted.

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