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Clinical performance of low-concentration bleaching gels with hyaluronic acid and NF_TiO_2 nanoparticles activated by violet LED: A randomized clinical trial

Priscila Borges Gobbo de Melo [a], Marcos Roberto de Lima Benati [a], Iago César Ribeiro Teles Matos [a], Guilherme Silva dos Santos [a], Matheus Kury [b], Fernando Luís Esteban Florez [c], Vanessa Cavalli [a,*]

[a] Department of Restorative Dentistry, University of Campinas - Piracicaba Dental School, Piracicaba, SP, Brazil
[b] Dental Division Research, Paulista University, São Paulo, SP, Brazil
[c] Department of Restorative Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, USA

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ABSTRACT

Objectives: To evaluate the bleaching efficacy, tooth sensitivity (TS), pulpal oxygen saturation (SaO_2), and patient satisfaction following in-office bleaching using experimental gels containing hyaluronic acid (HA) or carbomer 940 (CAR), co-doped TiO_2 nanoparticles with nitrogen and fluoride (NP; NF_TiO_2), and 6 % hydrogen peroxide (HP), activated by violet LED.

Methods: Seventy-two participants were randomly assigned to three groups (n = 24): HP35 (commercial bleaching gel), HA-NP-HP6+LED, and CAR-NP-HP6+LED. Bleaching was performed in three weekly sessions (1 × 30 min; 1-week interval). TS (VAS) and SaO_2 were recorded before and after each session, with TS reassessed seven days post-treatment. Tooth color was evaluated at baseline, 14 days, and 6 months post-treatment. The parameters ΔEab, ΔE_{00}, ΔWI_D, and ΔSGU were calculated. Patient satisfaction was assessed using a subjective scale. Statistical analysis was performed using one-way ANOVA with Tukey post hoc and non-parametric tests (α = 0.05).

Results: The HP35 group showed significantly higher bleaching efficacy after 14 days. However, at the 6-month evaluation, the experimental gels exhibited similar performance. TS was significantly lower in the experimental groups ($p < 0.05$), while SaO_2 levels remained stable across all groups. All participants (100 %) reported satisfaction with the outcomes.

Conclusions: Low-concentration bleaching gels containing 6 % hydrogen peroxide and NF_TiO_2 nanoparticles showed comparable efficacy to a 35 % hydrogen peroxide gel after 6 months, with less tooth sensitivity and no adverse effects on pulp oxygen saturation. Patient satisfaction was high across all groups, supporting the clinical viability of these safer experimental gels.

Clinical Relevance: Low-concentration gels enhanced with NF_TiO_2 nanoparticles and activated by violet LED may provide an effective and patient-centered bleaching option, maintaining long-term results while minimizing sensitivity.

1. Introduction

Tooth bleaching is a safe, effective, and minimally invasive procedure [1,2], widely employed to manage dental discoloration and improve both aesthetics and patient self-esteem [3,4]. This treatment has been continuously refined to enhance its efficacy, safety, and comfort [4]. Among the available techniques, in-office bleaching, typically performed using high concentrations of hydrogen peroxide (35–40 %), is

* Corresponding author at: Operative Dentistry Division, Department of Restorative Dentistry, State University of Campinas, Piracicaba Dental School, 901 Limeira Avenue, Piracicaba, São Paulo 13414-903, Brazil.
E-mail addresses: pribgobbo@gmail.com (P.B.G. de Melo), marcos.rbenati@hotmail.com (M.R.L. Benati), iagocrtm@gmail.com (I.C.R.T. Matos), gui.santos272001@gmail.com (G.S. Santos), matheuskury@hotmail.com (M. Kury), Fernando-esteban-florez@ouhsc.edu (F.L.E. Florez), cavalli@unicamp.br (V. Cavalli).

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distinguished by its professional supervision, which allows for greater application control and reduces the risk of soft tissue exposure [1,2]. Hydrogen peroxide (HP), the primary active agent, is highly effective in altering tooth color; however, it is frequently associated with the occurrence of tooth sensitivity [2,5–8].

Tooth sensitivity (TS), the most common adverse effect of bleaching [5–8], arises from the high diffusion capacity of HP through dental tissues, allowing it to reach the pulp chamber and trigger an inflammatory response in pulpal cells [7,9–13]. When excessive amounts of HP penetrate the pulp, cells release large quantities of inflammatory mediators into the tissue, leading to an inflammatory process [14–16]. Although typically transient, this discomfort is more prevalent in treatments involving high concentrations of HP [9–13]. Bleaching efficacy is strongly influenced by both the concentration and application time of HP, while higher concentrations provide faster results, they also increase the risk of tooth sensitivity and cellular stress [2,4,17,18].

To mitigate adverse effects, recent studies have focused on bleaching gels containing lower concentrations of HP, enhanced by promising technologies such as the incorporation of catalytic agents like titanium dioxide (TiO_2) [4,13,19,20]. TiO_2 is a chemically stable and biocompatible semiconductor, recognized for its strong oxidative potential and, notably, its photocatalytic activity under visible light, which can enhance bleaching efficiency in a safe and effective manner [13,20,21].

The use of nitrogen-doped titanium dioxide nanoparticles (N_TiO_2) has been investigated for their potential to maintain bleaching efficacy with reduced hydrogen peroxide concentrations (6–15 %) while significantly minimizing tooth sensitivity (TS) through their photocatalytic activity [4,13]. Traditionally, the photocatalytic activity of TiO_2 requires irradiation within the ultraviolet spectrum (UV-C, UV-B, or UV-A) to promote electrons excitation from the valence band to the conduction band, thereby initiating the generation of reactive oxygen species (ROS) [22]. In this context, the NF_TiO_2 nanoparticles employed in the present study demonstrate extended optical absorption into the violet range (390–420 nm), enabling violet LED irradiation (λ = 401.82 nm) to effectively accelerate HP dissociation and trigger subsequent reactions that generate superoxide anions (O_2^-), a type of long-lived ROS [23]. Furthermore, recent approaches have investigated titanium dioxide nanoparticles co-doped with nitrogen (N) and fluoride (F) (NF_TiO_2) at low concentrations, yielding promising outcomes in terms of both bleaching efficacy and cellular biocompatibility [12,19,20,23].

Thus, the photocatalytic properties of TiO_2 nanoparticles can be further exploited using specific light sources, such as violet LED, to enhance bleaching outcomes. Violet LED light (~ 405–410 nm) has emerged as a promising approach for dental bleaching, enhancing the action of HP gels. This light source promotes photochemical interactions with particles in the bleaching gel that are sensitive to this specific wavelength, such as titanium dioxide (TiO_2) [12,13,20]. Studies indicate that violet LED maintains efficacy comparable to high-concentration peroxide gels while producing lower tooth sensitivity, whereas blue LED performs poorly when used in combination with TiO_2 nanoparticles [24]. Despite these benefits, violet light presents certain limitations, including low enamel penetration, a heterogeneous beam profile, and reduced irradiance with increasing distance between the device and the tooth surface, factors that may compromise the predictability and uniformity of bleaching outcomes [25].

In addition to the active component, bleaching gels contain a thickening agent, typically a synthetic polymer such as carbomer 940 (CAR), a water-soluble polyacrylic acid polymer that effectively facilitates the delivery of ROS to the tooth surface [26,28]. However, its pH variability may negatively affect enamel morphology and structure [26,28]. As an alternative, biopolymers such as hyaluronic acid (HA) have garnered increasing interest in medical applications due to their favorable physiological characteristics, including biocompatibility, biodegradability, and bioactivity [29–31]. Although studies investigating the use of HA in dental bleaching remain limited, this biopolymer may offer dual benefits by stabilizing the bleaching gel and acting as a controlled-release vehicle for hydrogen peroxide, owing to its biodegradable nature [29–31]. Such properties may contribute to reduced tooth sensitivity and better preservation of enamel physicochemical integrity, positioning HA as a promising substitute for synthetic polymers.

The combination of low-concentration HP (6 %), co-doped TiO_2 nanoparticles (NP; NF_TiO_2), and violet LED activation (consisting of 20 one-minute irradiations interspersed with 30-second intervals, totaling 30 min of activation) has demonstrated promising in vitro results in tooth bleaching, maintaining bleaching efficacy, preserving enamel's physicochemical properties, and reducing cellular cytotoxicity [26,27]. However, randomized clinical trials are necessary to assess the performance of such bleaching gels, including color change, tooth sensitivity, and pulpal effects. To date, no prior randomized clinical trials have evaluated the bleaching efficacy, TS, and pulpal oxygen saturation levels (SaO_2) of gels containing HA and NF_TiO_2 nanoparticles.

This study aimed to assess the short-term (14 days) and long-term (6 months) bleaching efficacy, tooth sensitivity, SaO_2 levels, and participant satisfaction after in-office bleaching with experimental gels containing HA, CAR, NF_TiO_2 nanoparticles, and violet LED activation. The null hypotheses were that, compared to a commercial bleaching gel, the experimental formulations would show: (1) no difference in short-term bleaching efficacy; (2) no difference in long-term bleaching efficacy; (3) no increase in tooth sensitivity; (4) no changes in SaO_2 levels; and (5) no effect on participant satisfaction.

2. Materials and methods

2.1. Ethical approval and protocol registration

This clinical trial was approved by the Ethics Committee of the School of Dentistry at the University of Campinas (Piracicaba, SP, Brazil; approval number: 6.835.901) and registered with the Brazilian Clinical Trials Registry (ReBEC: RBR-75kq9s2). All participants were fully informed about the nature and objectives of the study, and written informed consent was obtained from each subject. All procedures were conducted in accordance with relevant guidelines and regulations.

2.2. Study design

The study was designed as a parallel, randomized, controlled, and double-blind clinical trial, following the Consolidated Standards of Reporting Trials (CONSORT) guidelines [32]. To ensure blinding, participants were unaware of the treatment group to which they had been assigned. Randomization and allocation concealment were performed by a designated member of the research team. Although the clinical operator administering the treatments was aware of the group assignments, all outcome assessors remained blinded to the procedures applied in each group.

2.3. Recruitment

Participants were recruited via social media, using visually appealing materials shared on Instagram® to highlight the eligibility criteria. Individuals who expressed interest contacted the research team for an initial screening. The recruitment strategy also involved sharing posts through the researchers' personal Instagram stories to enhance outreach through collaborative dissemination.

2.4. Eligibility criteria

Inclusion criteria: Participants aged between 18 and 35 years, with vital teeth, no periodontal disease, carious lesions, endodontic treatments, or edentulous spaces. Additionally, eligible participants were required to have good oral and general health, with both upper canines presenting a shade of A2 or darker according to the VITA Classical Shade

Guide (VITA Zahnfabrik, Bad Säckingen, Germany), and no restorations in the anterior teeth.

Exclusion criteria: Individuals with known adverse reactions to the materials used, teeth presenting extensive visible cracks, specific medical conditions (including pregnancy, lactation, or smoking), or pre-existing oral conditions such as non-vital teeth, the need for endodontic treatment, ongoing orthodontics therapy, or poor oral hygiene were excluded.

2.5. Sample size calculation

The sample size was calculated using the Sealed Envelope Ltd. 2012 calculator (https://www.sealedenvelope.com), based on the data reported by Bortolatto et al. [33], who evaluated a 15 % bleaching gel containing N_TiO nanoparticles and demonstrated significant bleaching efficacy. For the calculation, the mean shade reduction values of the experimental group (8.92) and the control group (6.66), with a standard deviation of 2.36, were considered after the final bleaching session. It was determined that 18 participants per group would be required to detect statistically significant differences between groups, with a significance level of 5 % ($p < 0.05$) and a statistical power of 80 %. To compensate for potential dropouts, 24 participants were allocated to each group.

2.6. Randomization, allocation, and blinding

Randomization was performed by a member of the research team who was not involved in either the bleaching procedures or evaluations. This person assigned a unique code to each participant, recorded it on a sheet, and placed it inside a sealed brown envelope. These envelopes were then randomly distributed among the three intervention groups, and the contents of each envelope were revealed to the operator only at the beginning of the first bleaching session.

Participants were blinded to the treatment received, as they were unaware of which bleaching gel had been applied. All participants, regardless of group allocation, wore protective dark glasses. In the group treated with 35 % hydrogen peroxide (commercial HP) without violet LED, the dark glasses were used, and the LED was turned on without directing it toward the tooth surface, solely to standardize application time. Additionally, participants were not informed of the differences between the groups.

Although the clinical operator was aware of the group allocation due to the visual differences between the gels, participants were prevented from seeing the materials, as an assistant assisted during application to ensure proper blinding. All evaluators responsible for outcome assessments remained blinded to group allocation, thereby ensuring unbiased analysis of the results.

2.7. Study intervention

Prior to treatment, all participants underwent dental prophylaxis. For proper isolation, the lips and tongue were protected using a lip retractor (Arcflex, FGM Dental Products, Joinville, SC, Brazil). This device also includes a tongue depressor that keeps the tongue away from the treatment area and allows the patient to gently bite down, ensuring greater comfort throughout the procedure. A light-curing resin-based gingival barrier (Top Dam, FGM, Joinville, SC, Brazil) was also applied to protect the soft tissues. To maintain blinding, participants wore dark protective glasses throughout the procedure, preventing them from identifying the bleaching gel used.

Three distinct in-office bleaching protocols were employed as interventions in this study. The groups were defined according to the bleaching gels used: (1) HP35, (2) HA-NP-HP6+LED, and (3) CAR-NP-HP6+LED. The HP35 gel was applied to the tooth surface for 30 min in a single application without violet LED irradiation. In both experimental groups, violet LED light (Bright Max Whitening – BMW (MMOptics, São Carlos, SP, Brazil), characterized by a 405 nm wavelength LED coupled to a curved acrylic tip) was used. The illumination area of the tip is 10.7 cm^2, with a maximum power of 22 VA and an optical power of 1.2 W. The irradiation cycle followed the manufacturer's guidelines, consisting of 1-minute irradiation intervals alternated with 30-second breaks, with the device positioned 8 mm from the dental arches. The complete cycle, including irradiation and breaks, totaled 30 min [34].

The experimental bleaching gels were prepared weekly in individual containers to ensure accurate weighing at a 2:1 ratio (%HP:gel), yielding final gels with a nanoparticle concentration of 5 % and a pH close to 6.0 [29]. After preparation, the containers were stored in a thermal container, protected from light, and refrigerated until use. Hydrogen peroxide was incorporated into the hydrogel immediately before application to the tooth surface. The composition of the experimental gels is presented in Table 1, while Table 2 summarizes the materials, their compositions, and the bleaching protocols employed.

2.8. Color analysis

Color evaluations were performed by two previously calibrated examiners, following the guidelines outlined in ISO/TR 28,642 (ISO/TR, 2011) [35]. Measurements were recorded at three time points: before bleaching (T_0), fourteen days after the final bleaching session (T_{14}), and six months post-treatment (T_{6m}). It is important to note that no prophylaxis was performed prior to the six-month evaluation.

An objective assessment of color change was performed using a digital spectrophotometer (VITA Easyshade, Vita Zahnfabrik, Bad Säckingen, Germany). To standardize the measurements, a high-density silicone impression (Perfil, Coltene, Rio de Janeiro, RJ, Brazil) of each participant's upper right arch was obtained beforehand [7,36].

A hole matching the dimensions of the spectrophotometer tip was created in the right canine region of the silicone mold, ensuring consistent evaluation areas at all time points [7,36]. Measurements were recorded using the CIELab* system, where L* represents lightness, and a* and b* represent the green-red and blue-yellow axes, respectively. Color change was calculated using the following formulas: $\Delta E_{ab} = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]\hat{}(1/2)$ [37], $\Delta E_{00} = [(\Delta L'/K\_LSL)^2 + (\Delta C'/K\_CSC)^2 + (\Delta H'/K\_HSH)^2 + RT^*(\Delta C'/K\_CSC)(\Delta H'/K\_HSH)]\hat{}(1/2)$ [36]. The 50:50 % perceptibility threshold (PT) adopted was 1.2 units for ΔE_{ab} and 0.8 units for ΔE_{00} [38], while the acceptability thresholds

Table 1
Composition of the experimental gels used in the study.

Experimental gels	Experimental material	Specification/Composition
HA-NP-HP6+LED	Hydrogel with hyaluronic acid as thickener	Hyaluronic acid (Sigma-Aldrich, St. Louis, MI, USA), ultrapure water, and potassium hydroxide
	Co-doped titanium dioxide nanoparticles	Ti (OBu)₄ (Aldrich, 97 %), C_2H_5OH (200-proof, Decon Labs, King of Prussia, PA, USA), $C_{18}H_{35}NH_2$ (Aldrich, 70 %), $C_{18}H_{34}O_2$ (Aldrich, 90 %), NH_4F (based on Ti content; crystalline, ACS, Alfa Aesar) and ethanol-water solution
	Hydrogen peroxide solution	6 % hydrogen peroxide solution (Sigma-Aldrich, St. Louis, MI, USA)
CAR-NP-HP6+LED	Hydrogel with carbomer 940 as thickener	Carbomer 940 NP (Spectrum, Gardena, CA), ultrapure water, and potassium hydroxide
	Co-doped titanium dioxide nanoparticles	$Ti(OBu)_4$ (Aldrich, 97 %), C_2H_5OH (200-proof, Decon Labs, King of Prussia, PA, USA), $C_{18}H_{35}NH_2$ (Aldrich, 70 %), $C_{18}H_{34}O_2$ (Aldrich, 90 %), NH_4F (based on Ti content; crystalline, ACS, Alfa Aesar) and ethanol-water solution
	Hydrogen peroxide solution	6 % hydrogen peroxide solution (Sigma-Aldrich, St. Louis, MI, USA)

Table 2
Bleaching gels, composition, and study protocols.

Bleaching gel	Specification/Composition	Study protocol
HA-NP-HP6+LED	Hyaluronic acid hydrogel containing 5 % co-doped titanium dioxide nanoparticles and a 6 % hydrogen peroxide solution, irradiated with violet LED light	Gingival tissues were protected with a light-curing resin-based gingival barrier (Top Dam, FGM, Joinville, SC, Brazil). This group combined the application of the experimental gel (applied once for 30 min) with a LED irradiation protocol at 7-day intervals. The bleaching protocol was performed in 3 sessions with 7-day intervals between them.
CAR-NP-HP6+LED	Carbomer 940 hydrogel containing 5 % co-doped titanium dioxide nanoparticles and a 6 % hydrogen peroxide solution, irradiated with violet LED light	
HP35 – Whiteness HP (FGM, Joinville, SC, Brasil)	35 % hydrogen peroxide, glycerol, inert filler, and deionized water; pH as specified by the manufacturer: 7.0	Gingival tissues were protected with a light-curing resin-based gingival barrier (Top Dam, FGM, Joinville, SC, Brazil). The 35 % hydrogen peroxide bleaching gel was applied once for 30 min. The bleaching protocol was performed in 3 sessions with 7-day intervals between them.

(AT) were set at 2.7 for ΔE_{ab} and 1.8 for ΔE_{00}. The bleaching index was calculated using the formula: $WI_D = 0.511\ L - 2.324a^* - 1.100b^*$ [39].

Additionally, changes in the whiteness index (ΔWI_D) were calculated by subtracting the values obtained at each evaluation stage from those recorded at the preceding stage. The 50:50 % perceptibility (WPT) and acceptability (WAT) thresholds for the whiteness index change were set at 0.72 and 2.60 ΔWI_D units, respectively [39].

2.9. Tooth sensitivity (TS)

Tooth sensitivity (TS) during and after the bleaching sessions was assessed using a visual analog scale (VAS; 0–10). During each session, the examiner asked the participants to rate the level of pain perceived immediately after the procedure using a score from 0 to 10 [34]. In the subsequent session, participants were again queried regarding the degree of sensitivity in the days following the previous session [34]. This protocol was consistently applied in all bleaching sessions, with an additional evaluation one week after the final session.

The assessments were performed by previously calibrated examiners, who remained blinded to the treatments. To avoid interference with the results, participants were instructed not to use any dentifrices specifically for reducing TS or any bleaching dentifrices during the study period. Participants who reported no sensitivity at any time were assigned a score of 0 [33], while those reporting at least a score of 1 were classified as sensitive to the intervention. Based on these data, both the risk and intensity of TS associated with each bleaching protocol were calculated [34].

2.10. Pulp oxygen saturation (SaO_2) analysis

The pulpal oxygen saturation (SaO_2) level was evaluated using a pulse oximeter adapted with a neonatal oximetry sensor (UT100 MD, Medjet, Joinville, SC), under isolation with cotton rolls and constant suction to ensure a dry surface and minimize light reflection [5,40]. Participants were positioned in a supine position and instructed to remain silent during the test [40]. The sensor, which featured a prefabricated adapter, was inserted into the tooth of interest such that the emitted light reached the middle third of the crown, with the emitter diode and photodetector arranged to accurately measure pulpal oxygen saturation [5,40]. The reading was obtained one minute after the sensor was placed on the tooth. This procedure was repeated both before and after each bleaching session, always under controlled ambient temperature. Measurements were performed by trained examiners who were blinded to the treatments [5,40].

2.11. Participant satisfaction evaluation

Participant satisfaction was assessed 14 days after the final bleaching session (T_{14}) in a well-lit area with sufficient natural light. A scoring scale was utilized to capture satisfaction with the tooth color after bleaching, where: 0 = dissatisfaction, 1 = basic satisfaction, 2 = satisfaction and 3 = complete satisfaction [41,42]. Participants were instructed to select the number that best represented their opinion.

2.12. Statistical analysis

The objective color evaluation data were analyzed for normality and homogeneity of variances using the Shapiro–Wilk and Levene tests, respectively. The exploratory analysis indicated that the variables ΔE_{ab}, ΔE_{00}, and ΔWI_D (T_{14}–T_0 and T_{6m}–T_0) met the criteria for normal distribution and homogeneity of variances ($p > 0.05$). Consequently, a one-way ANOVA was performed, followed by Tukey's post hoc test for multiple comparisons among the groups. Subjective color change data (ΔSGU) were analyzed using non-parametric tests for multiple comparisons, specifically the Kruskal–Wallis and Dunn tests. For sensitivity and pulpal oximetry analyses, non-parametric Kruskal–Wallis and Dunn tests were used for comparisons among treatments, and the Friedman and Nemenyi tests were employed for comparisons over time. The Chi-square and Fisher's Exact tests were applied to evaluate the risk of sensitivity. Statistical analyses were performed using SPSS software (version 26.0, IBM, Chicago, IL, USA) and GraphPad Prism (version 9.0, GraphPad, San Diego, CA, USA), adopting a significance level of 5 %.

3. Results

3.1. Volunteer characteristics

Recruitment was conducted between November 2023 and February 2024. Clinical examinations were conducted on 100 potential participants, and 72 volunteers ($n = 24$ per group) were included in the study. The flow of participants throughout the clinical trial and the number of dropouts per intervention group are illustrated in Fig. 1. The participants' characteristics and baseline values are presented in Table 3. Bleaching sessions were performed from March to May 2024, with no dropouts recorded during the treatment. Both short-term (14 days) and long-term (6 months) follow-ups were conducted after the final bleaching session. At the six-month evaluation, two participants withdrew from the study, both due to relocation. All volunteers who underwent the intervention ($n = 72$) were assessed for the primary outcome (color change) and the secondary outcomes (tooth sensitivity, SaO_2, and satisfaction). No adverse events, unintended effects, or study-related harms were observed in any of the groups during the study period.

3.2. Color analysis

Fig. 2 presents the mean values and corresponding standard deviations of the analyses for ΔE_{ab} and ΔE_{00} during both the short-term and long-term follow-up periods. Fig. 3 displays the median values and interquartile ranges for the subjective analysis (ΔSGU). All bleaching protocols demonstrated ΔE values greater than 1.2. The HP35 treatment produced the greatest color change (ΔE and ΔSGU) at the 14-day interval ($p < 0.001$), followed by the CAR-NP-HP6+LED and HA-NP-HP6+LED treatments, which did not differ significantly from each other ($p = 0.728$). However, after 6 months, the experimental groups

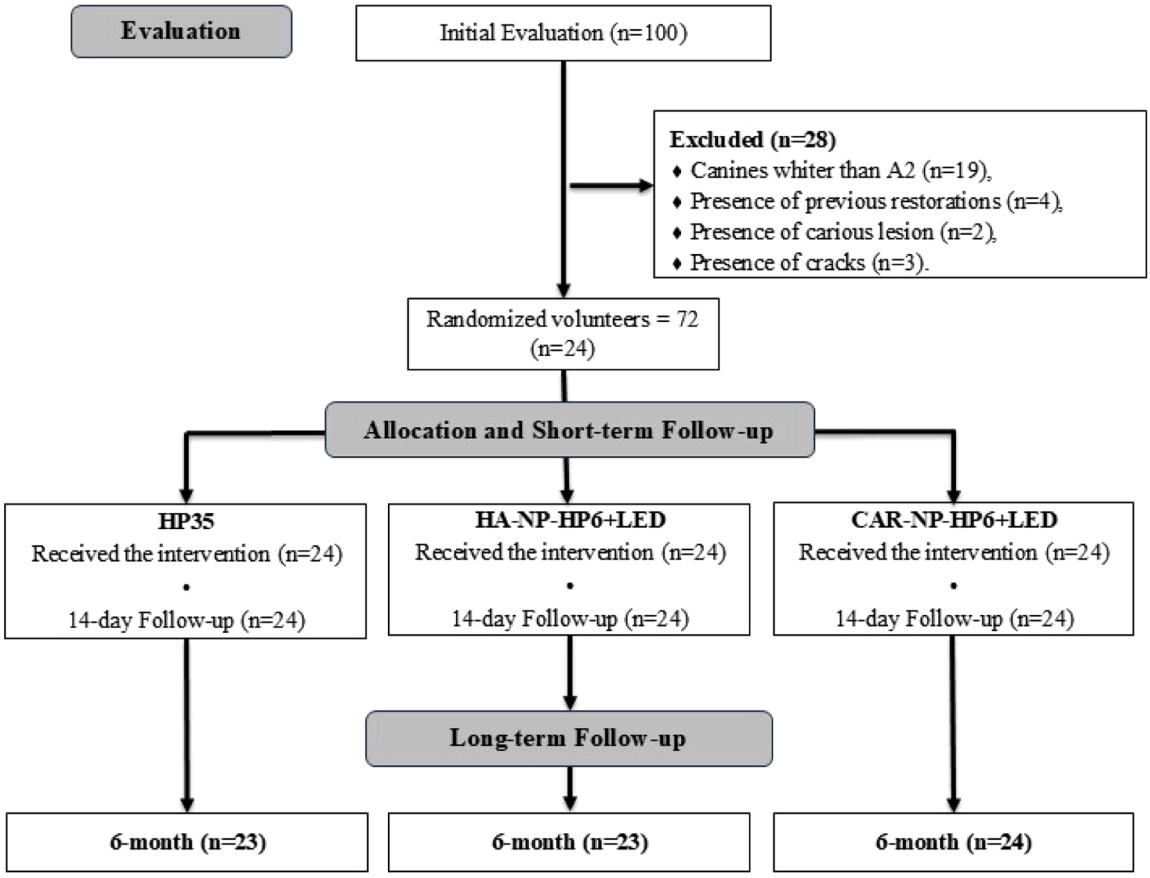

Fig. 1. CONSORT Flow Diagram Constructed According to Eligibility Criteria.

Table 3
Baseline values of the CIELab coordinates and main descriptive characteristics of the participants included in the study.

		HP35	HA-NP-HP6+LED	CAR-NP-HP6+LED
Coordinate values (Mean, SD)				
*L		79.71 (3.85)	80.82 (3.61)	80.82 (3.43)
*a		−0.11 (1.13)	−0.53 (0.74)	0.29 (0.91)
*b		26.24 (2.74)	26.21 (2.82)	26.72 (2.74)
SGU (Vita Classical)		8.75 (2.29)	8.12 (2.75)	8.5 (2.55)
Age in years (Mean, SD)		21.56 (3.26)		
Gender (%)	Male	33,34 %		
	Female	66,66 %		

(CAR-NP-HP6+LED and HA-NP-HP6+LED) achieved the same color change as the HP35 treatment for the ΔE ($p = 0.130$) and ΔWI_D ($p = 0.075$) analyses, with no statistically significant differences.

All groups showed mean ΔE_{ab} and ΔE_{00} values above the 50:50 % perceptibility threshold (ΔE>1.2). The mean ΔSGU values, as well as those of ΔE_{ab} and ΔE_{00}, exhibited distinct patterns over time. These patterns varied across different treatments. The CAR-NP-HP6+LED and HP35 treatments demonstrated similar color changes, with no statistically significant differences between them during the long-term follow-up (T_{6m}). In contrast, the HA-NP-HP6+LED group presented a lower ΔSGU compared to the HP35 group at the same time point (T_{6m}).

Fig. 4 illustrates the mean ΔWI_D values assessed 14 days and 6 months after the final bleaching session. The HP35 treatment yielded the highest whiteness index among all groups at the 14-day mark ($p < 0.001$). In contrast, no statistically significant differences were observed between the CAR-NP-HP6+LED and HA-NP-HP6+LED treatments ($p = 0.929$). At the 6-month follow-up, all bleaching protocols exhibited statistically comparable ΔWI_D values, with no significant differences detected among the groups. All mean ΔWI_D values exceeded the 50:50 % perceptibility threshold.

3.3. Tooth sensitivity (TS)

TS was assessed up to 7 days after the final bleaching session. Both the risk and intensity of sensitivity were evaluated before and after each bleaching session. A significant association was found between the bleaching treatments and the risk of TS ($p < 0.05$) at the following time points: after the first session, before the second session, before and after the third session, and 7 days after the final session (Table 4). Participants treated with HP35 showed significantly higher risk of developing TS compared to those in the other groups ($p < 0.01$).

Table 5 presents the results for the intensity of TS. Sensitivity scores were significantly higher in the HP35-treated group compared to the other groups ($p < 0.05$) before the 2nd and 3rd sessions, as well as 7 days after the last session. Furthermore, the HP35-treated group showed a significant variation in sensitivity scores over time ($p < 0.001$), with higher values before the 2nd and 3rd sessions, and 7 days after the last session, when compared to baseline ($p < 0.05$). On the other hand, the groups treated with CAR-NP-HP6+LED and AH—NP-HP6+LED did not show significant variations in sensitivity scores over time ($p > 0.86$)

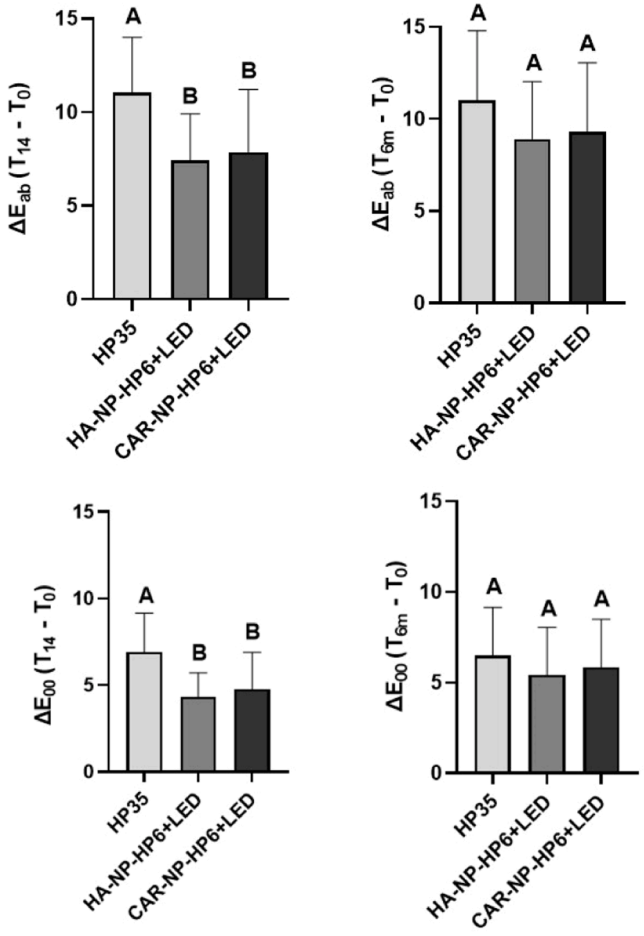

Fig. 2. Means and standard deviations of the objective color changes (ΔE_{ab} and ΔE_{00}) evaluated 14 days and 6 months after the final bleaching session. Means accompanied by different letters indicate statistically significant differences at a 5 % level. Uppercase letters indicate comparisons among the different bleaching protocols within the same evaluation period.

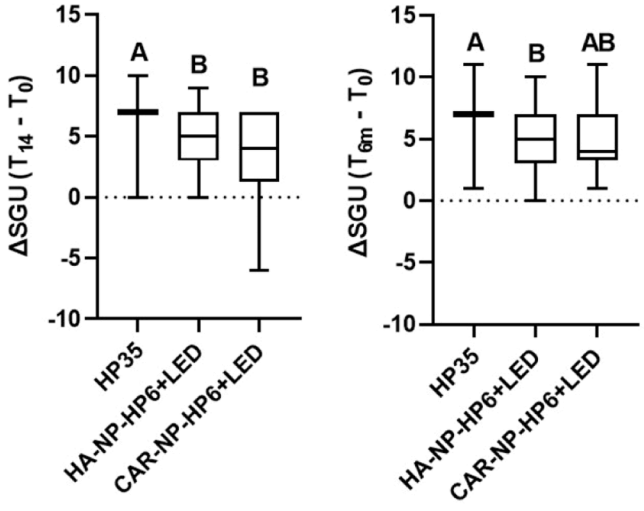

Fig. 3. Box plot of subjective color changes (ΔSGU) showing the median, interquartile ranges, and minimum and maximum values assessed at 14 days and 6 months after the final bleaching session. Medians followed by different letters indicate statistically significant differences at the 5 % level. Uppercase letters compare different bleaching protocols within the same evaluation period.

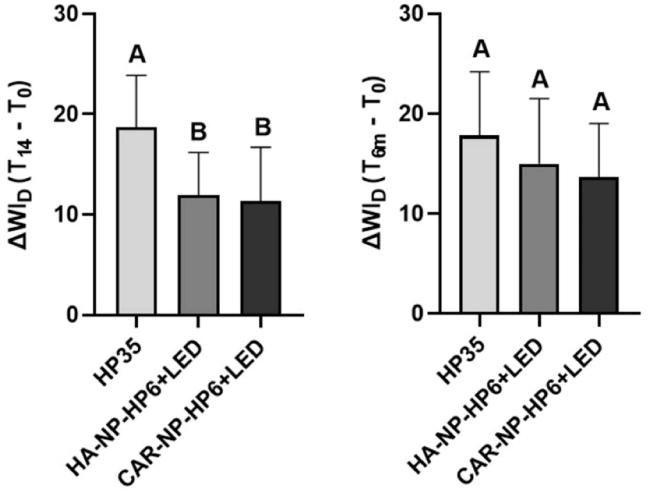

Fig. 4. Mean values and standard deviations of the whiteness index (ΔWI_D) assessed 14 days and 6 months after the final bleaching session. Means followed by different letters indicate statistically significant differences at the 5 % level. Uppercase letters denote comparisons among the different bleaching protocols within the same evaluation period.

Table 4
Risk of tooth sensitivity according to the bleaching treatment.

Time	HP35	HA-NP-HP6+LED	CAR-NP-HP6+LED	p-value
	Frequence (%)			
Baseline	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	–
After 1st session	11 (45.8 %)	3 (12.5 %)	3 (12.5 %)	0.0072
Before 2nd session	16 (66.7 %)	3 (12.5 %)	5 (20.8 %)	0.0001
After 2nd session	5 (20.8 %)	3 (12.5 %)	3 (12.5 %)	0.7732
Before 3rd session	20 (83.3 %)	3 (12.5 %)	6 (25.0 %)	<0.0001
After 3rd session	9 (37.5 %)	3 (12.5 %)	2 (8.3 %)	0.0300
7 days after final session	15 (62.5 %)	3 (12.5 %)	3 (12.5 %)	<0.0001

Chi-square and Fisher's Exact tests ($p < 0.001$). HP35 – group treated with commercial 35 % hydrogen peroxide (Whiteness HP, FGM); HA-NP-HP6+LED – group treated with an experimental gel containing hyaluronic acid as a thickener, NF_TiO_2 nanoparticles, 6 % hydrogen peroxide, and irradiated with violet LED; CAR-NP-HP6+LED – group treated with an experimental gel containing carbomer 940 as a thickener, NF_TiO_2 nanoparticles, 6 % hydrogen peroxide, and irradiated with violet LED.

3.4. Analysis of pulp oxygen saturation (SaO_2)

Table 6 presents the results of the comparison of SaO_2 levels across different reading periods, before and after the application of the bleaching gels. No significant differences were observed ($p > 0.08$) when evaluating each bleaching gel individually over time. Similarly, when comparing the different bleaching gels within the same time period, no significant differences were found ($p > 0.22$).

3.5. Participant satisfaction analysis

The data presented in Table 7 show the number and percentage of participants who reported satisfaction/dissatisfaction after the bleaching treatment. For analysis purposes, participants were classified as dissatisfied if they assigned a score of 0 (dissatisfaction) on the evaluation questionnaire. The results suggest that there was no variation in satisfaction levels between the different treatments evaluated, as all

Table 5
Sensitivity intensity based on treatment and time.

Time	HP35	HA-NP-HP6+LED	CAR-NP-HP6+LED	p-value
	Median (minimum and maximum)			
Baseline	0 (0–0) ^{Ac}	0 (0–0) ^{Aa}	0 (0–0) ^{Aa}	1.0000
After 1st session	0 (0–9) ^{Aabc}	0 (0–6) ^{Aa}	0 (0–7) ^{Aa}	0.1550
Before 2nd session	1.5 (0–9) ^{Aab}	0 (0–4) ^{Ba}	0 (0–5) ^{Ba}	0.0017
After 2nd session	0 (0–10) ^{Abc}	0 (0–6) ^{Aa}	0 (0–4) ^{Aa}	0.8082
Before 3rd session	2 (0–7) ^{Aa}	0 (0–6) ^{Ba}	0 (0–6) ^{Ba}	<0.0001
After 3rd session	0 (0–8) ^{Aabc}	0 (0–4) ^{Aa}	0 (0–3) ^{Aa}	0.1520
7 days after final session	2.5 (0–8) ^{Aab}	0 (0–7) ^{Ba}	0 (0–7) ^{Ba}	0.0042
p-value	<0.0001	0.9905	0.8619	–

Medians followed by different letters are statistically different at the 5 % significance level, as determined by the Kruskal-Wallis and Dunn tests for treatment comparisons, and the Friedman and Nemenyi tests for time comparisons. Uppercase letters compare treatments, while lowercase letters compare evaluation times.

Table 6
Analysis of pulp oxygen saturation (SaO_2), by treatment and time.

Time	HP35	HA-NP-HP6+LED	CAR-NP-HP6+LED	p-value
	Median (minimum and maximum)			
Baseline	82 (75; 100)	85 (70; 100)	83.5 (70; 97)	0.7683
After 1st session	81 (70; 100)	85.5 (72; 99)	83.5 (71; 100)	0.3310
Before 2nd session	81 (73; 89)	80 (70; 95)	81 (70; 100)	0.6983
After 2nd session	80.5 (71; 100)	81 (70; 100)	83 (70; 96)	0.2209
Before 3rd session	79 (72; 94)	80 (70; 89)	83 (70; 100)	0.2547
After 3rd session	80.5 (70; 91)	80.5 (70; 97)	78 (70; 97)	0.9652
p-value	0.3521	0.0832	0.4960	–

Medians followed by different letters differ statistically at the 5 % significance level, according to the Kruskal-Wallis and Dunn tests for comparisons between treatments, and the Friedman and Nemenyi tests for comparisons between time points.

Table 7
Participants satisfied/dissatisfied after treatments.

Treatments	Dissatisfaction	Basic satisfaction	Satisfaction	Full satisfaction
HP35	0	2 (8.33 %)	9 (37.5 %)	13 (54.17 %)
HA-NP-HP6+LED	0	2 (8.33 %)	9 (37.5 %)	13 (54.17 %)
CAR-NP-HP6+LED	0	3 (12.5 %)	7 (29.17 %)	14 (58.33 %)

0 = Dissatisfaction, 1 = Basic satisfaction, 2 = Satisfaction and 3 - Full satisfaction.

participants reported satisfaction, regardless of the treatment received.

4. Discussion

The results of this clinical trial indicate that the group treated with the commercial bleaching gel (HP35) exhibited a statistically greater color change compared to the experimental gels in the short term, leading to acceptance of the first null hypothesis. However, the second null hypothesis was rejected, as the bleaching efficacy of the experimental gels (CAR-NP-HP6+LED and HA-NP-HP6+LED) was comparable to HP35 in the long term. Perceptible ($\Delta E_{00} > 0.8$) and acceptable ($\Delta E_{00} > 1.8$) color changes [38] were observed across all evaluated time points, with similar results noted at the 6-month follow-up.

Although the HP35 group showed higher bleaching efficacy during the first 14 days, the experimental gels containing low concentration of HP achieved equivalent results in the long term, as indicated by ΔE and ΔWI_D values. These findings corroborate previous studies that emphasize the role of NF_TiO_2 nanoparticles in enhancing the efficacy of low-concentration bleaching gels [26,27]. Moreover, the ΔE and ΔWI_D analyses confirm that the experimental treatments maintained comparable bleaching efficacy to the HP35 group after 6 months. From a clinical standpoint, this suggests that gels with lower HP concentrations may provide a viable alternative by reducing the risks of adverse effects without compromising bleaching outcomes [4,13,33,43].

The mechanism of in-office teeth bleaching involves the diffusion of hydrogen peroxide through the dental structure, leading to the formation of reactive oxygen species (ROS). These free radicals, characterized by their short lifespan and high reactivity, are efficiently transported from the bleaching gel to the dentin-enamel junction, where they break the conjugated double bonds in large organic molecules via a non-specific oxidative process [9,19]. The incorporation of NF_TiO_2 nanoparticles into low-concentration bleaching gels enhances this mechanism, as these nanoparticles absorb visible light wavelengths and generate longer-lasting ROS [17]. Consequently, NF_TiO_2 nanoparticles are believed to remain active even after gel removal, contributing to a residual bleaching effect and prolonging color stability up to 6 months by continuously producing stable and persistent ROS. This sustained generation, amplified by the interaction between the nanoparticles and violet light during treatment, promotes more effective oxidation of the chromophores responsible for dental pigmentation, thereby aiding in the maintenance of the bleaching effect.

The present study provides clinical evidence that complements the in vitro findings of de Benati et al. [12], demonstrating that the incorporation of hyaluronic acid (HA) as a thickening agent in bleaching gels confers consistent benefits without compromising treatment efficacy. Previous in vitro studies reported that HA-containing gels enhanced ΔWI_D outcomes, preserved enamel physicochemical properties [20], and displayed low cytotoxicity [12,20]. The current clinical results corroborate these findings, showing that HA maintains bleaching efficacy equivalent to carbomer (CAR) gels and the commercial gel (HP35), while ensuring stable tooth sensitivity, preserving SaO_2 levels, and promotes patient satisfaction. Collectively, these results highlight the role of HA in optimizing the gel rheology and protecting dental tissues, supporting its safe and practical application in low-concentration hydrogen peroxide bleaching protocols combined with violet LED activation.

Building on these clinical observations, the bioadhesive properties of hyaluronic acid (HA) within the enamel matrix may enable prolonged interaction between the NF_TiO_2 nanoparticles and the enamel surface, supporting a sustained photocatalytic effect and reducing the re-incorporation of new pigments. Additionally, HA contributes to moisture retention and protects against microstructural damage, both of which are essential for maintaining bleaching stability by preventing enamel opacification and loss of translucency over time [30]. Thus, it is suggested that the interaction between HA and NF_TiO_2 nanoparticles in the bleaching gel not only provides an immediate bleaching effect but also ensures the long-term maintenance of the color change, with perceptible results sustained even after 6 months.

Color changes were calculated using the CIELab (ΔE_{ab}), CIEDE2000 (ΔE_{00}), and Whiteness Index for Dentistry (WI_D) systems [36–39], based on the L*, a*, and b* parameters. Among these, the CIEDE2000 system is preferred due to its higher accuracy in reflecting visual color perception [43], while the WI_D provides complementary insights into the direction of the bleaching effect [39]. Both methods are widely employed in

clinical trials, and in this study, the observed values were consistent with the clinically relevant thresholds for perceptibility (PT) and acceptability (AT) 50:50 [39]. In addition to objective analyses, a subjective shade assessment method was used, which, despite being influenced by individual perception, holds significant clinical relevance [8]. In this context, the CAR-NP-HP6+LED group exhibited performance comparable to the HP35, reinforcing the clinical viability of this bleaching treatment.

While this is not the first randomized clinical trial (RCT) to investigate low-concentration bleaching gels containing with TiO_2 nanoparticle [4,13,30], it is the first to develop and apply bleaching gels using NF_TiO_2 nanoparticles, as well as using HA as a thickening agent. Previous studies offer important context for interpreting these findings [4, 13,33], underscoring the novelty of the present work and its potential implications for clinical dentistry.

This innovation is particularly relevant considering the unique properties of titanium dioxide (TiO_2), which stands out for its high oxidative potential, chemical stability, antimicrobial activity, and biocompatibility, and has therefore been extensively investigated in dental applications [44–46]. To further enhance these properties, structural modification approaches such as co-doping with nitrogen (N) and fluoride (F) have been explored [44,47]. Nitrogen reduces the band gap, improving light absorption in the visible spectrum, although it may also create oxygen vacancies that promote electron–hole recombination. Conversely, fluoride stabilizes surface bonds, decreasing recombination events and enhancing the generation of ROS, which are crucial for dental bleaching. Consequently, N/F co-doping provides complementary advantages, extending the photocatalytic activity of TiO_2 and reinforcing its clinical efficacy [44,47].

In the experimental groups, TS was significantly lower at all evaluated time points compared to the HP35, resulting in the acceptance of the third null hypothesis. This reduction in sensitivity may be attributed to the lower HP concentration and the presence of NF_TiO_2 nanoparticles, which efficiently absorb visible light wavelengths and promote the generation of significant amounts of superoxide radicals (O_2^-), thereby reducing the formation of radical species commonly associated with TS [20]. Moreover, the increase in HP concentration is directly associated with greater TS, leading to a higher susceptibility to this adverse effect, corroborating the findings of this study [10,11,14].

These results are consistent with findings by Bortolatto et al., [13], who reported reduced sensitivity rates when using 6 % HP combined with N_TiO_2 nanoparticles and LED irradiation. Moreover, the incorporation of NF_TiO_2 nanoparticles, along with the use of low HP concentration, enhances the biocompatibility of the bleaching gels [19,20, 24], which may have contributed to the observed reduction in TS during and after treatment. In this context, Kury et al. [19] demonstrated that NF_TiO_2 nanoparticles irradiated with violet LED, when combined with 6 % HP, reduced the trans-enamel-dentin diffusion of HP, minimized oxidative stress, and significantly increased cell viability. These effects ultimately led to a reduction in inflammatory responses within the pulp chamber, which are directly associated with the occurrence of TS [19].

Another relevant factor contributing to the reduced TS observed in the experimental groups was the use of hyaluronic acid as a carrier matrix. Owing to its biodegradability and capacity to form a structured matrix, hyaluronic acid enables the controlled release of ROS from the bleaching gel to the dental structure. This gradual release mitigates the cytotoxicity effects typically associated with bleaching procedures, thereby leading to a lower incidence of TS [29–31].

The fourth null hypothesis was accepted. Although a reduction in SaO_2 levels was observed throughout the treatment, no statistically significant differences were found among the evaluated groups. These results suggest that both the experimental treatments and HP35 did not compromise pulp vitality. This finding is crucial for confirming the safety of protocols involving low HP concentration and violet LED activation, indicating that the application of the experimental gels did not induce significant alterations in pulp microcirculation, as previously reported [5,40].

Although no specific studies in the literature have evaluated SaO_2 levels following in-office bleaching using low concentrations of HP combined with TiO_2 nanoparticles, the present findings are supported by previous studies that assessed SaO_2 levels during conventional in-office bleaching procedures [5,15]. Lima et al. [15] and Bacaksiz et al. [5] both reported a reduction in SaO_2 levels during in-office bleaching, consistent with the results observed in this study. These findings reinforce the clinical relevance e of the present data and highlight the safety of the experimental treatments in terms of preserving pulp vitality.

Additionally, all patients reported satisfaction with the bleaching treatments, with 50 % of individuals, regardless of the protocol used, reporting complete satisfaction with the outcomes. This finding supported the rejection of the fifth null hypothesis. The result may be attributed to the subjective nature of participants' perception of bleaching efficacy, which can be influenced by personal expectations, previous experiences, and individual aesthetic standards [41,42]. Furthermore, the comfort provided by the experimental gels, particularly due to the lower incidence of TS, may have further contributed to participants' overall satisfaction with the bleaching treatment.

The pursuit of low-concentration bleaching gels that preserve bleaching efficacy has garnered growing interest among researchers. This interest is driven by concerns regarding the potential cytotoxic effects of high-concentration bleaching gels on pulp cells, which may result in tooth sensitivity [11,19]. In this context, recent randomized clinical trials have evaluated the performance of a low-concentration commercial gel containing nitrogen-doped titanium dioxide nanoparticles (N_TiO, Nano White 6 %, DMC), in combination with LED [33, 43]. The results of these studies demonstrated significant reductions in TS incidence compared to high-concentration gels, corroborating the findings of the present study.

Although promising, the results have limitations that should be acknowledged. In this study, all bleaching gels were applied over three clinical sessions, regardless of HP concentration. Increasing the number of sessions for groups treated with lower HP concentrations could potentially enhance their bleaching efficacy compared to the commercial bleaching gel, without increasing the risk of tooth sensitivity. Moreover, the use of low-concentration gels represents a promising approach for future investigations. Long-term clinical trials are needed to explore different combinations of catalytic agents and HP concentrations, with the goal of further optimizing dental bleaching protocols.

5. Conclusions

In-office teeth bleaching using low-concentration gels containing NF_TiO_2 nanoparticles proved to be as efficacious as the commercial 35 % hydrogen peroxide gel over a 6-month period, while significantly reducing the risk and intensity of tooth sensitivity. Moreover, no significant differences in pulp oxygen saturation levels were detected among the treatment groups, indicating the safety of these formulations. Overall, all participants expressed satisfaction with the bleaching outcomes regardless of the protocol applied, demonstrating the clinical viability and patient acceptance of the experimental gels.

Ethics approval

This study did not need ethical approval.

Consent to participate

This study did not need informed consent.

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CRediT authorship contribution statement

Priscila Borges Gobbo de Melo: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marcos Roberto de Lima Benati:** Methodology, Conceptualization. **Iago César Ribeiro Teles Matos:** Methodology, Conceptualization. **Guilherme Silva dos Santos:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Matheus Kury:** Methodology, Data curation, Conceptualization. **Fernando Luís Esteban Florez:** Resources, Methodology, Funding acquisition, Conceptualization. **Vanessa Cavalli:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Vanessa Cavalli reports financial support was provided by São Paulo Research Foundation. Fernando Luis Esteban Florez has patent pending to Licenciado. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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