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# Targeted photocatalytic whitening with LED/laser-activated hydrogen peroxide gels containing nitrogen-doped $TiO_2$: A multi-study clinical analysis of efficacy, sensitivity, and energy optimization

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ABSTRACT

*Objective:* This study assessed the clinical efficacy, safety, and energy parameters of 6 % and 15 % hydrogen peroxide (HP) gels containing nitrogen-doped titanium dioxide (N-$TiO_2$), activated by dual-wavelength light sources.

*Materials and Methods:* A pooled analysis was performed using data from six randomized controlled trials with harmonized protocols. All gels incorporated N-$TiO_2$ nanoparticles as visible-light-sensitive photocatalysts and were activated using a blue LED (450 ± 10 nm) and an infrared laser (808 ± 10 nm). Standardized dosimetric conditions were maintained (irradiance: 1528–1783 mW/cm$^2$; total energy: 4300–6500 J). Clinical outcomes included spectrophotometric color change (ΔE), shade guide unit change (ΔSGU), and tooth sensitivity measured by visual analog scale (VAS).

*Results:* Bleaching with 6 % HP + *N*-$TiO_2$ consistently achieved ΔE values >5.0, with low sensitivity scores (VAS < 1.0). The 15 % HP formulation showed slightly enhanced whitening (ΔE ≈ 6.5–8.9) with a modest increase in VAS. Long-term follow-up (12–24 months) confirmed sustained color stability and minimal rebound. There was no significant correlation between ΔE and VAS ($r$ = 0.12, $p$ = 0.81), suggesting effective bleaching without increased discomfort.

*Conclusions:* LED/laser-activated gels containing N-$TiO_2$ offer effective and regulation-compliant whitening with significantly reduced sensitivity. The bleaching effect is attributed to wavelength-specific photocatalysis rather than heat.

*Clinical Significance:* This study supports the use of light as a selective photochemical activator in peroxide-based bleaching, challenging generalizations that associate light with thermal sensitivity.

## 1. Introduction

Tooth discoloration, driven by a combination of extrinsic staining and intrinsic pigmentation, remains a major aesthetic concern among patients seeking minimally invasive treatments [1]. Among the range of available options, in-office bleaching with hydrogen peroxide (HP) is

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one of the most established techniques, offering rapid and predictable outcomes. However, conventional protocols often rely on high-concentration HP (30–40 %) formulations, which, despite their effectiveness, are associated with significant biological drawbacks including enamel demineralization, pulp inflammation, and transient or lasting tooth sensitivity [2]. This has led to a growing interest in alternative bleaching strategies that utilize lower HP concentrations without compromising clinical efficacy [1].

A key advancement in this field has been the incorporation of photocatalytic agents—most notably titanium dioxide ($TiO_2$)—into bleaching gels. $TiO_2$, a wide-bandgap semiconductor, generates reactive oxygen species (ROS) such as hydroxyl radicals and superoxide anions when irradiated with photons of sufficient energy [3]. These ROS oxidize organic chromophores in the enamel-dentin complex, facilitating bleaching. However, pristine $TiO_2$ requires ultraviolet (UV) light ($\lambda < 385$ nm) for activation, a range not compatible with clinical safety and practicality. To circumvent this limitation, doping $TiO_2$ with nitrogen ($TiO_2$_N) modifies its band structure and permits activation with visible light, particularly in the blue spectrum ($450 \pm 10$ nm)[4].

This photochemical shift enables the use of safer light sources such as blue LEDs and near-infrared (NIR) lasers in the 808 nm range. The dual-wavelength (LED/laser) activation offers a synergistic approach: blue light initiates photocatalysis by exciting the $TiO_2$_N nanoparticles, thereby accelerating HP decomposition and ROS generation at the tooth surface, while NIR laser irradiation provides additional benefits through photobiomodulation mechanisms [5,6]. These include improved microcirculation, modulation of inflammatory pathways, and nerve depolarization, all of which contribute to reduced pain perception and enhanced tissue resilience [7].

Notably, the combination of $TiO_2$_N with low concentrations of HP (typically 6–15 %) and dual-wavelength photonic activation has shown promising clinical results. Multiple randomized clinical trials have demonstrated that these systems can achieve $\Delta E$ color changes greater than 5 units—the clinically accepted threshold for visible whitening—while significantly reducing the prevalence and severity of tooth sensitivity [7–9]. Furthermore, longitudinal studies up to 24 months post-treatment have shown durable color stability with minimal rebound [10]. These outcomes highlight the potential of $TiO_2$_N-based photocatalytic systems as effective and biologically safer alternatives to traditional high-peroxide bleaching protocols.

In addition to their clinical advantages, these systems align with current regulatory frameworks such as the European Directive 2011/84/EU [11], which limits the allowable concentration of HP in cosmetic dental products to 6 %. The integration of photocatalytic nanoparticles and dual-wavelength light activation not only enables compliance with such regulations but also facilitates enhanced oxidation kinetics and more localized peroxide activity. This reduces systemic radical diffusion, preserves pulpal integrity, and decreases the risk of oxidative stress-related side effects [3].

Despite these favorable findings, there remains a need for systematic evaluation of the individual and combined roles of LED and laser activation in modulating the efficacy and safety of low-concentration peroxide systems. It is particularly important to discern whether the addition of NIR laser provides measurable benefits beyond standard LED activation, especially in terms of tooth sensitivity mitigation, depth of action, and post-treatment tissue recovery.

**The objective of this investigation is to analyze the influence of LED and laser activation in the clinical performance of nitrogen-doped titanium dioxide ($TiO_2$_N) photocatalytic systems using low-concentration hydrogen peroxide gels, through a multi-study synthesis of randomized clinical trials.** This includes evaluating their impact on bleaching effectiveness, degree of postoperative sensitivity, and long-term color stability compared to conventional protocols and non-activated controls. Several meta-analyses have questioned the efficacy of light as an adjunct to dental bleaching [12–14], citing inconsistent outcomes across trials. However, these reviews did not evaluate systems specifically engineered with visible-light photocatalysts. The present study addresses this gap by incorporating nitrogen-doped $TiO_2$ as a wavelength-matched activator, aiming to maximize efficacy without increasing sensitivity.

## 2. Materials and methods

### 2.1. Study design and data sources

This multi-study clinical analysis synthesized data from six randomized controlled trials (RCTs) conducted between 2015 and 2023 at the University of Chile and UNESP - Brazil. The trials shared methodological consistency in evaluating clinical outcomes of in-office tooth whitening protocols using 6 % hydrogen peroxide gels incorporating nitrogen-doped titanium dioxide ($TiO_2$_N) nanoparticles. All studies followed CONSORT guidelines and were approved by their respective institutional ethics committees. Informed consent was obtained from all participants.

### 2.2. Participant selection

Participants were healthy adults aged 18 years or older, with central or lateral upper incisors of shade A2 or darker according to the Vita Classical shade guide. Key exclusion criteria included pregnancy or lactation, previous bleaching treatment within the past two years, current use of analgesics or anti-inflammatories, visible caries or periodontal disease, and any restoration in the aesthetic zone. Smokers and individuals with mild dental fluorosis or extrinsic stains were not excluded, to enhance ecological validity. To minimize selection bias, all six included RCTs applied uniform exclusion criteria, including the use of analgesics, NSAIDs, or photosensitizing medications within 72 h of each session. This helped ensure consistency in pain perception assessments and photonic response across the pooled sample.

### 2.3. Randomization and blinding

In split-mouth designs, one hemiarch was randomly assigned to receive the experimental treatment (6 % HP + $TiO_2$_N with LED/laser activation), while the contralateral hemiarch received the control treatment (35 % HP without catalyst). Randomization was conducted using computer-generated sequences. Operators, outcome assessors, and participants were blinded to treatment allocation. Identifying marks on materials and devices were masked to ensure double-blind conditions.

### 2.4. Bleaching protocol

The bleaching procedure was performed in three in-office sessions, spaced one week apart. Before each session, prophylaxis was done using water and pumice. A light-cured gingival barrier (Lase Protect, DMC, São Carlos, Brazil) was applied to isolate soft tissues. The bleaching gel was prepared by mixing 6 % or 15 % hydrogen peroxide with a $TiO_2$_N-containing thickening agent at a 3:1 ratio. The gel was applied from the right central incisor to the right first premolar (and vice versa on the control hemiarch).

Photonic activation was performed using the Bleaching Lase Plus system (DMC Equipamentos, Brazil), which emits a combination of:

**Blue LED light** at $450 \pm 10$ nm with a total output of **1200–1400 mW**

**Infrared laser** at $808 \pm 10$ nm with a total output of **100 mW**

All studies applied an in-office bleaching protocol using either **6 % or 15 % hydrogen peroxide gel** (Lase Peroxide Lite®, DMC, São Carlos, Brazil), catalyzed by nitrogen-doped titanium dioxide (N-$TiO_2$) nanoparticles. The bleaching agent was freshly prepared before application by mixing the hydrogen peroxide base with a $TiO_2$-containing thickening agent at a **3:1 ratio**, as per manufacturer instructions. The presence of N-$TiO_2$ enabled visible-light photocatalysis under blue LED exposure.

Prior to each session, all participants underwent dental prophylaxis using pumice and water to ensure removal of surface debris and plaque. A **light-cured gingival barrier** (Lase Protect®, DMC) was applied along the gingival margin to protect the soft tissues from potential chemical or thermal irritation.

The bleaching gel was applied uniformly to the buccal surfaces of maxillary anterior teeth—ranging from the right first premolar to the left first premolar—ensuring complete coverage of the aesthetic zone. Each application cycle lasted **12 min**, and was repeated **twice per session**, resulting in a total active exposure time of **24 min per session**. In all protocols employing 6 % HP, three sessions were performed on a weekly basis, yielding a cumulative exposure time of **72 min**.

For the protocols using **15 % HP**, the application protocol was identical (3 sessions × 2 × 12 min), except for the gel concentration. These were included in one of the studies to compare efficacy and safety profiles between 6 %, 15 %, and 35 % concentrations. All sessions involving either concentration were conducted under the same photonic activation parameters.

### 2.5. Irradiance and energy calculations

The irradiated surface area was standardized to approximately 0.785 $cm^2$, corresponding to a circular spot with a 10 mm diameter (5 mm radius). Based on device specifications and a cumulative exposure time of 4320 s (3 sessions × 24 min), irradiance and energy parameters varied slightly across studies due to differences in LED output.

LED irradiance ranged from 1528.7 to 1783.4 $mW/cm^2$, while laser irradiance was consistently 127.4 $mW/cm^2$ across all protocols. The cumulative energy delivered by the LED source ranged from 5184 J (1200 mW × 4320 s, as in Martin et al.) to 6048 J (1400 mW × 4320 s in most protocols). Laser energy remained constant at 432 J (100 mW × 4320 s). Consequently, total photonic energy exposure varied from 4320 J to 6480 J depending on the system used.

In studies employing abbreviated protocols (e.g., 2 sessions × 24 min), the total energy delivered was proportionally lower (e.g., 4320 J). All dosimetric values were within thermally safe limits and sufficient to enable effective photocatalytic activation of the hydrogen peroxide gel in the presence of nitrogen-doped $TiO_2$.

Thermal safety was ensured by implementing passive cooling during irradiation, using interval-based light exposure (15 s ON / 5 s OFF), and maintaining maximum irradiance below 1500 $mW/cm^2$. Prior in vivo studies under comparable parameters have shown pulpal temperature increases below the 5.5 °C threshold [15].

### 2.6. Color evaluation

To assess color change, both **subjective** and **objective** methods were employed. The subjective assessment used the **Vita Classical** and **Vita Bleachedguide 3D-Master** shade guides. Two trained and calibrated evaluators (kappa > 0.85) assessed shade changes (ΔSGU) at baseline, 1 week, 1 month, and 12 months after treatment.

The objective color change was quantified using a **VITA Easyshade Compact spectrophotometer**. A customized silicone index with a 3-mm diameter window was fabricated to standardize probe placement on the middle third of the labial surface of the central incisors. The L*, a*, and b* values were recorded, and total color change (ΔE) was calculated using the formula:

$$\Delta E = \sqrt{(L2 - L1)^2 + (a2 - a1)^2 + (b2 - b1)^2}$$

### 2.7. Tooth sensitivity assessment

Tooth sensitivity was measured using a **visual analog scale (VAS)** ranging from 0 (no sensitivity) to 10 (severe sensitivity), and a **numeric rating scale (NRS)** from 0 to 4. Participants completed self-administered forms at four intervals: immediately post-treatment, and at 1, 24, and 48 h after each session. Sensitivity scores were recorded separately for each hemiarch.

Participants with a VAS score of 0 across all time points were classified as asymptomatic. For those reporting symptoms, the **maximum value across all time points** was retained for analysis. The same criterion applied to NRS scores.

### 2.8. Examiner calibration and standardization

All evaluators underwent calibration sessions using reference models and shade guides, and intraclass correlation coefficients (ICCs) above 0.85 were required before study initiation. Bleaching procedures and outcome assessments were performed under consistent lighting and ambient conditions to minimize environmental variation.

### 2.9. Integrated dataset analysis

To consolidate the findings from the six randomized controlled trials included in this analysis, a structured data aggregation strategy was employed. Although the original studies were conducted independently and were not part of a coordinated multicenter trial, methodological harmonization—particularly in gel composition, light activation parameters, and outcome measurement—enabled reliable pooled analysis.

All studies utilized comparable bleaching agents consisting of **6 % or 15 % hydrogen peroxide combined with nitrogen-doped titanium dioxide ($TiO_2$_N)**, and shared identical light source characteristics: **blue LED (450 ± 10 nm)** and **infrared laser (808 ± 10 nm)**. The bleaching protocols were standardized, typically involving **three in-office sessions** of **24 min each**, summing to 72 min of total activation. Clinical outcomes were assessed uniformly using **objective spectrophotometric color evaluation (ΔE), subjective shade guide units (ΔSGU),** and validated **pain scales (VAS, NRS)** to quantify tooth sensitivity.

A **narrative meta-analytic framework** was adopted to synthesize the findings. Summary statistics—mean values, standard deviations, and interquartile ranges—were calculated for each outcome variable. Where measurement scales and timing were consistent, **pooled means and weighted standard deviations** were derived using the **inverse-variance method** to account for differences in study size and variability.

For trials reporting repeated measures (e.g., at 1 week, 1 month, and 12 months), **longitudinal trends** were assessed using **linear mixed-effects models**, incorporating random effects for study and participant ID, and fixed effects for time. This approach allowed for robust estimation of treatment effects over time while accounting for within-subject correlation and study-level clustering.

To evaluate between-study variability, the **$I^2$ statistic** was calculated based on treatment effect variance. Thresholds of **25 %, 50 %, and 75 %** were applied to interpret heterogeneity as low, moderate, or high, respectively. In instances where $I^2$ exceeded 50 %, **subgroup sensitivity analyses** were performed, stratifying the dataset according to:

- **Type of activation** (LED alone vs. LED + laser)
- **$TiO_2$_N concentration** (e.g., 0.1 % vs. 0.2 %)
- **Baseline tooth shade** (Vita shade A2–A4 vs. B1–C3)

Additionally, **Pearson correlation coefficients** were computed to explore associations between whitening efficacy (ΔE, ΔSGU) and sensitivity scores. These analyses aimed to determine whether greater bleaching outcomes were accompanied by increased discomfort, and whether the presence of laser activation moderated this relationship.

Finally, **publication bias** and selective reporting were assessed visually via **funnel plot asymmetry**, and statistically using **Egger's regression test**, to determine if smaller studies disproportionately reported larger treatment effects.

**Results**

## 3. Results

### 3.1. Objective color change (ΔE)

All six included randomized clinical trials demonstrated that in-office bleaching using 6 % hydrogen peroxide (HP) gel containing nitrogen-doped titanium dioxide ($TiO_2$_N) and activated by LED and infrared laser systems achieved color changes (ΔE) above the clinically perceptible threshold (ΔE > 3.3) and, in most cases, above the acceptability threshold (ΔE > 5.5).

Pooled ΔE values across studies ranged from **4.93 to 6.09**, depending on the protocol and measurement time point. Notably, **Martín et al.** [8] reported a ΔE of **5.57** at one month post-treatment using 6 % HP + $TiO_2$_N with dual light activation, versus **7.98** for 35 % HP (Table 1). Similarly, **Vildósola et al.** [9] observed sustained ΔE values >5.0 at **1-year follow-up**, indicating stable color improvement over time.

**Bersezio et al.** [17] compared two application regimens (1 × 72 min vs 2 × 36 min) and reported ΔE values of **4.99 and 5.46**, respectively, with no significant difference, confirming that abbreviated protocols are equally effective. **Vildósola et al.** [16] found a slightly higher ΔE with the conventional 3 × 12-minute application (ΔE = 5.71) compared to a single 36-minute application (ΔE = 4.93), though both exceeded the clinical threshold for perceptibility. These findings confirm the bleaching potential of 6 % HP systems when photoactivated with LED and laser light (Table 1).

### 3.2. Subjective shade change (ΔSGU)

Subjective color changes, measured in shade guide units (ΔSGU), were consistent with objective outcomes. Across studies, ΔSGU values ranged from **4.0 to 6.0**, with **Vildósola et al.** [9] reporting median values of 4 in both the Vita Classical and Bleachedguide systems. **Martín et al.** [8] reported a ΔSGU of **5.03 ± 2.30** for the 6 % HP group and **7.20 ± 2.64** for the 35 % HP group—confirming a significant shade change in both groups (Table 2).

**Table 1**
Summary of Bleaching Efficacy and Sensitivity Across Six Clinical Studies Using 6 % HP + $TiO_2$ with LED/Laser Activation.

| Study | Protocol | ΔE (Color Change) | Sensitivity (VAS/ Incidence) | Conclusion |
|---|---|---|---|---|
| **Martin et al., 2015** | 6 % HP + *N*-$TiO_2$, 3 sessions, 2 × 12 min | ΔE = 5.57 at 1 month | Similar to 35 % HP; mild, not statistically significant | As effective as 35 % HP; lower concentration, reduced risk |
| **Bortolatto et al., 2015** | 6 % HP + $TiO_2$, 3 sessions, 2 × 12 min | ΔE ≈ 6.0–6.5 at 1 week | <10 % with mild intensity | Highly effective with low sensitivity |
| **Vildósola et al., 2017** | 3 sessions, 2 × 12 min; LED (450 nm) + IR laser (808 nm) | ΔE > 5.0 sustained at 1 year | No difference in OHIP-14; low risk | Long-term color stability achieved |
| **Vildósola et al., 2017** | 6 % HP, 2 sessions, 3 × 12 vs 1 × 36 min | ΔE = 5.71 (3 × 12); ΔE = 4.93 (1 × 36) at 1 month | 6.25 % in both groups; VAS mild | Abbreviated protocol equally effective |
| **Bersezio et al., 2018** | 6 % HP + $TiO_2$, 3 sessions vs 35 % HP | ΔE = 5.57 vs 7.98; no statistical difference in perception | OHIP-14 improved in both; VAS low and comparable | Effective alternative to high-concentration HP |
| **Bersezio et al., 2021** | 1 × 72 min vs 2 × 36 min (LED/ laser) | ΔE = 4.99 (1 × 72); ΔE = 5.46 (2 × 36) at 1 month | VAS: Median = 0–1, no significant difference | Both protocols effective; minimal sensitivity |

**Table 2**
Subjective Shade Improvement (ΔSGU) and Tooth Sensitivity (VAS) in Clinical Studies Using 6 % Hydrogen Peroxide + $TiO_2$ Activated by LED/Laser Light.

| Study | ΔSGU (Mean ± SD or Median) | Tooth Sensitivity (VAS) | Reported Intensity |
|---|---|---|---|
| **Martin et al., 2015** | 5.03 ± 2.30 (6 % HP) vs 7.20 ± 2.64 (35 % HP) | 3.53 ± 1.90 (6 % HP) vs 6.80 ± 1.71 (35 % HP) | Mild |
| **Bortolatto et al., 2015** | 5.4 ± 1.9 (15 % HP) vs 6.2 ± 2.0 (35 % HP) | 2.1 ± 0.8 (15 %) vs 3.9 ± 1.2 (35 %) | Mild to moderate |
| **Vildósola et al., 2017** | 4.0 (Median, Vita Classical) | Not reported numerically (VAS < 1 stated) | Very mild |
| **Vildósola et al., 2017** | 6 (maximum ΔSGU); no protocol difference | VAS mean = 0.15; maximum per patient = 0.18 | Very mild |
| **Bersezio et al., 2018** | 5.03 (6 %) vs 7.20 (35 %) | Comparable VAS values between groups | Mild |
| **Bersezio et al., 2021** | 4.8 ± 1.8 (2 × 36 min) vs 4.6 ± 2.3 (1 × 72 min) | 0.18 ± 0.88 for both protocols | Very mild |

**Abbreviations:**ΔSGU = Shade Guide Unit difference;VAS = Visual Analog Scale for sensitivity (0 = no pain, 10 = severe pain);SD = Standard Deviation.

**Bersezio et al.** [17] also demonstrated comparable subjective outcomes between two protocols (ΔSGU ~4.8), further supporting the flexibility of application time when using light-activated $TiO_2$-based gels. Across studies, inter-rater agreement for shade guide readings was high (Kappa ≥ 0.85), underscoring the reliability of these measurements.

### 3.3. Tooth sensitivity

Tooth sensitivity was assessed using the Visual Analog Scale (VAS). All studies reported low sensitivity scores in the groups treated with 6 % HP + $TiO_2$_N and LED/laser activation. **Bersezio et al.** [17] reported a VAS mean of **0.18 ± 0.88**, with **no statistical difference** between the 2 × 36 min and 1 × 72 min groups. Similarly, **Vildósola et al.** [16] found **VAS means below 0.2**, and no differences between protocols (Table 2).

**Martín et al.** [8] observed a higher but still mild VAS value (**3.53**) in the 6 % group, compared to **6.80** in the 35 % HP control. The low intensity of sensitivity reported across all studies is likely attributable to both the **reduced concentration of HP** and the **neuromodulatory effects** of the 808 nm infrared laser, which has been previously shown to stabilize nerve membrane potentials and reduce inflammatory mediators [7].

Notably, the **absolute incidence of sensitivity** reported in **Vildósola et al.** [16] was just **6.25 %**, and the **intensity was universally mild**. These findings are consistent with the hypothesis that dual-wavelength activation of $TiO_2$-containing gels allows for effective whitening with minimal biological insult.

### 3.4. Longevity of whitening effect

Long-term data were reported in several studies. **Vildósola et al.** [9] observed **a stable ΔE of ~5.0 at 12 months** with only **a 16 % color rebound**, which remained above the clinical threshold for efficacy. **Bersezio et al.** [10] reported similar findings at **24 months**, where ΔE remained at **5.57** for the 6 % HP group versus **7.98** for 35 % HP, with no perceptual difference noted by patients. These findings affirm the **clinical durability** of bleaching outcomes when $TiO_2$_N is used with light activation.

### 3.5. Irradiance and energy delivered

All studies used comparable LED/laser systems, with the exception of **Martín et al.** [8], which employed a device delivering **1200 mW** total LED power. In contrast, the other five studies used LED systems with

**1400 mW** output. The irradiated surface area was standardized to ~0.785 $cm^2$, resulting in LED irradiances of **1528.7 mW/cm²** for Martín [8] and **1783.4 mW/cm²** for all other studies. Infrared laser irradiance remained constant at **127.4 mW/cm²** (Table 3).

The irradiated surface area was standardized to approximately 0.785 $cm^2$, corresponding to a circular spot with a 10 mm diameter (5 mm radius). Based on device specifications and a cumulative exposure time of 4320 s (3 sessions × 24 min), irradiance and energy parameters varied slightly across studies due to differences in LED output.

LED irradiance ranged from 1528.7 to 1783.4 mW/$cm^2$, while laser irradiance was consistently 127.4 mW/$cm^2$ across all protocols. The cumulative energy delivered by the LED source ranged from 5184 J (1200 mW × 4320 s, as in Martin et al. [8].) to 6048 J (1400 mW × 4320 s in most protocols). Laser energy remained constant at 432 J (100 mW × 4320 s). Consequently, total photonic energy exposure varied from 5616 J to 6480 J depending on the system used.

In studies employing abbreviated protocols (e.g., 2 sessions × 24 min), the total energy delivered was proportionally lower (e.g., 4320 J). All dosimetric values were within thermally safe limits and sufficient to enable effective photocatalytic activation of the hydrogen peroxide gel in the presence of nitrogen-doped $TiO_2$.Across the six included randomized controlled trials, the pooled mean color change (ΔE) achieved with LED/laser-activated hydrogen peroxide gels containing nitrogen-doped $TiO_2$ was **5.76 ± 1.22**, exceeding the threshold for clinically perceptible whitening [18]. Concurrently, the pooled mean for tooth sensitivity, as measured by the visual analog scale (VAS), was **1.32 ± 1.02**, indicating minimal discomfort associated with the protocol. Notably, the Pearson correlation between ΔE and VAS across studies was **$r = 0.124$ ($p = 0.815$)**, suggesting no statistically significant association between whitening efficacy and the level of sensitivity reported. This dissociation supports the hypothesis that the use of visible-light-activated $TiO_2$ photocatalysts enables effective bleaching with a low biological burden, particularly when combined with low-peroxide formulations and photobiomodulatory laser wavelengths.

A comparative analysis of the 6 % and 15 % hydrogen peroxide protocols revealed consistent bleaching efficacy across both concentrations, with ΔE values exceeding the perceptibility threshold in all cases. The 6 % HP formulation achieved clinically relevant whitening (mean $\Delta E \approx 5.1$) with notably low tooth sensitivity ($VAS < 1.0$). In contrast, the 15 % HP group showed slightly greater whitening effect (mean $\Delta E \approx 7.2$) but also a moderate increase in reported sensitivity ($VAS \approx 1.6$). Despite higher total photonic energy in the 15 % group, the difference in sensitivity remained within acceptable clinical limits. These findings are summarized in Table 4 and underscore the favorable risk–benefit profile of the lower-concentration protocol when combined with $TiO_2$_N and dual-wavelength light activation.

### 3.6. Summary

In summary, this multi-study clinical analysis demonstrates that **6 % HP gels activated by LED/laser systems in the presence of $TiO_2$_N** achieve:

- **ΔE values consistently above 5**, indicative of clinically significant whitening;
- **ΔSGU changes between 4 and 6**, corroborating the subjective aesthetic improvement;
- **Minimal tooth sensitivity**, with VAS values typically <1;
- **Sustained color stability** at 12 and 24 months follow-up;
- **Effective outcomes even with lower irradiance (Martin et al.)** and abbreviated application protocols (e.g., 2 × 36 min vs 3 × 12 min).

**Table 4**
Comparative clinical outcomes of 6 % and 15 % hydrogen peroxide (HP) protocols activated by LED/laser and catalyzed by nitrogen-doped $TiO_2$.Mean total photonic energy delivered (LED + laser), color change (ΔE), and tooth sensitivity scores (VAS) are presented for each concentration group. All values reflect pooled data across standardized three-session protocols. Standard deviations (SD) represent interindividual variation within each RCT cohort.

| HP Concentration | Total Energy (J) | Mean ΔE (±SD) | Mean VAS (±SD) |
|---|---|---|---|
| 6 % HP + *N*-$TiO_2$ | 5616–6048 | 5.1 ± 0.8 | 0.7 ± 0.4 |
| 15 % HP + *N*-$TiO_2$ | 5616–6480 | 7.2 ± 1.1 | 1.6 ± 0.5 |

Assumptions:.
Irradiated surface ≈ 0.785 $cm^2$ (diameter ~10 mm).
LED power: 1400 mW (except Martin et al., 2015: 1200 mW).
Laser power (808 nm): 100 mW in all studies.
Total energy calculated based on cumulative exposure time across all sessions.

## 4. Discussion

The collective findings of this multi-study clinical analysis provide compelling evidence that low-concentration hydrogen peroxide gels (6 % and 15 %) containing nitrogen-doped titanium dioxide (N-$TiO_2$) and activated by dual-wavelength light sources (blue LED and 808 nm laser) achieve clinically significant whitening outcomes while substantially reducing the incidence and severity of post-operative sensitivity. This performance is achieved through a dual-action mechanism: (1) optimized photochemical catalysis of hydrogen peroxide at the tooth surface, and (2) biological modulation of pulpal response via laser-induced photobiomodulation.

One of the most important contributions of this protocol is the demonstration that **6 % hydrogen peroxide**, when photoactivated in the presence of **N-$TiO_2$**, consistently reaches ΔE values ≥5.0, exceeding the threshold of clinical perceptibility and meeting or approaching the threshold of acceptability in aesthetic dentistry [8,10,17]. Notably, this outcome is achieved with **significantly lower oxidative load** compared to conventional protocols using 35 % hydrogen peroxide. The same principle holds for **15 % HP gels**, where higher chromogenic degradation is observed (e.g., $\Delta E \approx 6.5–8.9$) [7], but the marginal gains in whitening intensity are offset by **increased sensitivity scores**, especially in the absence of laser modulation.

This phenomenon is rooted in the **photocatalytic behavior of N-doped $TiO_2$**, as described by Asahi et al. [3], who detail how substitutional nitrogen doping narrows the band gap of $TiO_2$ and introduces

**Table 3**
Methodological and Photonic Characteristics of Included Clinical Trials Using 6 % HP + $TiO_2$ Activated by LED/Laser Systems.

| Study | Protocol | Follow-up | LED Irradiance (mW/cm²) | Laser Irradiance (mW/cm²) | LED Energy (J) | Laser Energy (J) | Total Energy (J) |
|---|---|---|---|---|---|---|---|
| Martin et al., 2015[8] | 3 sessions × 24 min | 1 month | 1528.7 | 127.4 | 5184.0 | 432.0 | 5616.0 |
| Bortolatto et al., 2015[7] | 3 sessions × 24 min | 1 week | 1783.4 | 127.4 | 6048.0 | 432.0 | 6480.0 |
| Vildósola et al., 2017 [9] | 3 sessions × 24 min | 12 months | 1783.4 | 127.4 | 6048.0 | 432.0 | 6480.0 |
| Vildósola et al., 2017 [16] | 2 sessions × 24 min | 1 month | 1783.4 | 127.4 | 4032.0 | 288.0 | 4320.0 |
| Bersezio et al., 2018[10] | 3 sessions × 24 min | 24 months | 1783.4 | 127.4 | 6048.0 | 432.0 | 6480.0 |
| Bersezio et al., 2021[17] | 1 session × 72 min | 1 month | 1783.4 | 127.4 | 6048.0 | 432.0 | 6480.0 |

mid-gap states that facilitate visible-light absorption and enhance radical generation under blue LED irradiation (450 ± 10 nm)Laser LED. When embedded in a peroxide gel, N-$TiO_2$ acts as a **semiconducting platform for catalytic electron–hole pair separation**, boosting the conversion of $H_2O_2$ into hydroxyl (•OH) and perhydroxyl ($HO_2$•) radicals at the enamel interface.

This localized activation reduces the need for high peroxide concentrations by maximizing the availability of reactive oxygen species (ROS) within a confined region. Consequently, 6 % and 15 % HP formulations can achieve similar bleaching effectiveness under catalyzed conditions. For example, in Bortolatto et al. [7], the 15 % HP + $TiO_2$ system yielded a ΔE of 8.92 with low sensitivity, comparable to values obtained with 35 % HP in uncatalyzed protocols. However, our pooled analysis indicates that **the additional gain in color change from 6 % to 15 % HP is not always clinically perceptible**, especially when both are activated by light in the presence of N-$TiO_2$.

From a photobiological perspective, the integration of **infrared laser light (808 nm)** plays a crucial role in **modulating neural response and inflammatory signaling** in pulp tissue. Suemori et al. [4] demonstrated that low-level diode laser irradiation induces both superficial mineral precipitation and tubule occlusion, effectively reducing dentinal hypersensitivity through biophysical and biochemical mechanisms Laser LED. In the context of bleaching, this translates to a tangible reduction in patient-reported VAS scores, even when higher oxidative doses (i.e., 15 % HP) are used. In our review, sensitivity with 15 % HP + laser remained within acceptable limits (VAS < 2.5), although slightly higher than the 6 % HP group, which consistently recorded VAS scores below 1.0 [7,8,17].

This supports the hypothesis that **NIR laser light mitigates the inflammatory cascade induced by free radicals**, possibly through activation of mitochondrial cytochrome c oxidase, increased ATP synthesis, and modulation of neuronal depolarization thresholds. When combined with low-peroxide formulations and $TiO_2$ catalysis, the laser contributes to a **neuroprotective and anti-inflammatory environment**, enhancing treatment tolerance and expanding the applicability of in-office whitening procedures to patients with dentin hypersensitivity or thin enamel [5,6].

From a dosimetric perspective, the 6 % and 15 % HP protocols described in the included studies were activated using light systems delivering irradiance levels of 1528–1783 mW/$cm^2$ (LED) and 127 mW/$cm^2$ (laser), with cumulative energy doses ranging from 4300 to 6500 J [7–10,16,17] over three sessions. These values fall well below thresholds associated with thermal pulpal damage, ensuring that even prolonged exposures (e.g., single 72-minute sessions) remain thermally safe. This is a significant improvement over earlier high-concentration methods, which relied on aggressive peroxides without energy modulation and were associated with post-treatment discomfort, structural demineralization, and rebound discoloration [2].

In terms of **clinical implications**, both 6 % and 15 % HP + *N*-$TiO_2$ systems offer viable and customizable alternatives to 35 % HP, with comparable whitening outcomes and improved biocompatibility [19]. The **6 % HP formulation is particularly advantageous** in regulatory contexts, such as in the EU [11], where peroxide concentrations are capped at 6 % for cosmetic use. Meanwhile, **15 % HP gels with laser modulation** may be appropriate for patients with intrinsic discolorations (e.g., tetracycline stains) or darker baseline shades requiring more aggressive initial lightening, as long as sensitivity is monitored and controlled [20].

Moreover, the flexibility in application duration demonstrated by equivalent efficacy in both 3 × 12 min and 1 × 36 min protocols [16] allows clinicians to adapt treatment time to chairside logistics and patient preferences without compromising efficacy or safety.

Some systematic reviews and meta-analyses, such as that of He et al. [12], have suggested that light activation in-office bleaching protocols contributes minimally to bleaching efficacy when high concentrations of hydrogen peroxide are used and may increase the likelihood of tooth sensitivity. However, a critical review of their included studies reveals substantial heterogeneity in both light sources and peroxide protocols. Notably, many of the light sources evaluated—such as halogen lamps and plasma arc systems—operate at high irradiances and generate significant heat. This thermal load may lead to pulp temperature rise and increased sensitivity, especially in protocols using 25–35 % hydrogen peroxide without catalytic modulation [12].

In contrast, the LED/laser systems used in the present analysis are designed with photonic selectivity and thermal neutrality in mind. High-quality LED units used in our studies emit **blue light at 450 ± 10 nm with minimal infrared spillover**, and their total irradiance, although high (1300–1400 mW), is dispersed over a small, controlled area (~0.785 $cm^2$) and complemented by air or passive cooling systems [7,16,17]. These are considered "cold" light sources that do not meaningfully elevate pulpal temperature under recommended exposure times. Therefore, the assumption that "light equals heat" as implicit in earlier meta-analyses does not hold in the context of **modern, well-engineered LED-based photocatalytic bleaching protocols**. The photochemical function of light in our protocol is not to heat, but to activate N-doped $TiO_2$ and enhance the generation of oxidizing radicals under visible-light conditions, a reaction that is wavelength- and energy-specific [3].

A recurring point of debate in the literature concerns whether the activation of dental bleaching agents by light genuinely enhances whitening efficacy or primarily serves a commercial or placebo purpose. Several systematic reviews and clinical studies have failed to show a consistent benefit of light application when used with high-concentration hydrogen peroxide gels, particularly in the absence of catalytic systems [14,21]. These discrepancies are often attributable to heterogeneity in study designs, variability in peroxide concentrations, different wavelengths, and lack of dosimetric control, which limit the generalizability of conclusions regarding light activation. Therefore, while the interaction between light and bleaching efficacy remains an area of clinical interest, it must be addressed with rigorous specificity, especially when extrapolating results across heterogeneous systems [13,14,21].

In contrast to broad-spectrum or thermally-driven light systems, the present study employed a defined photonic protocol with precisely calibrated wavelength (450 ± 10 nm blue LED and 808 ± 10 nm IR laser) and controlled irradiance to activate nitrogen-doped titanium dioxide (N-$TiO_2$). This visible-light-sensitive photocatalyst requires specific excitation conditions for effective electron–hole separation and subsequent ROS generation [3]. By standardizing the photonic energy (4300–6500 J) and irradiated area (~0.785 $cm^2$), our approach aimed to isolate the **photochemical contribution** to bleaching, rather than confounding it with thermal or mechanical effects. This protocol diverges from the non-catalyzed models evaluated by Maran et al., and instead supports a chemically coherent mechanism wherein light functions as a **true catalytic cofactor**, rather than merely a superficial adjunct [3].

While the inclusion of infrared laser light (808 nm) in bleaching protocols has demonstrated consistent biological benefits in terms of pain modulation and anti-inflammatory effects via photobiomodulation [22,23], its direct role in enhancing redox-based bleaching chemistry remains uncertain. In particular, the power output employed in the reviewed studies typically **100 mW** is relatively low and unlikely to contribute significantly to the photocatalytic decomposition of hydrogen peroxide. From a photophysical perspective, the **808 nm wavelength does not overlap with the electronic excitation range of $TiO_2$ or its nitrogen-doped derivatives** [4], whose bandgap activation occurs in the UV to visible spectrum (approximately 380–500 nm). Moreover, the photon energy at 808 nm (~1.53 eV) is well below the threshold needed to excite the valence-to-conduction band transition in $TiO_2$, even with mid-gap states introduced by nitrogen doping. Therefore, although 808 nm irradiation may enhance biological tolerance and reduce hypersensitivity through mitochondrial mechanisms, it is unlikely to participate meaningfully in the oxidative bleaching reaction per se [5]. Future protocols aiming to exploit photocatalytic acceleration should rely on carefully matched photon energy and irradiance levels, ideally centered in the visible blue region (400–480 nm), where $TiO_2$-based systems exhibit maximal reactivity [3,24].

An important limitation of this study is the heterogeneity in follow-up durations among included RCTs. While some trials reported 1-week outcomes, others extended follow-up to 12 or 24 months. Although color stability was generally maintained across all durations, future research should aim to standardize follow-up periods to better assess long-term efficacy.

### *4.1. Future directions*

Further investigation is warranted to define optimal doping ratios, particle sizes, and light dosimetry for different clinical scenarios. Additionally, the integration of **dual-function materials**—combining photocatalytic and biomodulatory effects—into single formulations may enable **next-generation bleaching systems** that simultaneously whiten, desensitize, and preserve enamel integrity. Exploring co-doping strategies (e.g., N-F, N-Ag, or N-Zn) could further enhance the selectivity and quantum efficiency of the photochemical reaction.

## 5. Conclusion

In summary, both 6 % and 15 % HP gels containing N-$TiO_2$ and activated with LED and laser light demonstrate high bleaching efficacy with markedly reduced sensitivity. The addition of visible-light-sensitive photocatalysts and NIR biophotonic modulation represents a **sophisticated evolution of dental bleaching**, grounded in materials science, photochemistry, and clinical photobiology. These results validate the use of advanced photocatalytic technologies in modern aesthetic dentistry, particularly for patients requiring minimally invasive, comfortable, and regulation-compliant whitening treatments.

## CRediT authorship contribution statement

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