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The 1064-nm Nd:YAG Photobiomodulation vs. 20% Benzocaine Topical Gel in Inducing Mucosal Anesthetic Effect: A Double-Blind Randomized Clinical Trial

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Abstract: The periapical local anesthetic injection may be associated with fear of needles and pain administration. Dental topical anesthetic agents can help to reduce pain perception; however, adverse events can occur. To investigate the efficacy of 1064-nm photobiomodualtion (PBM) in inducing mucosal anesthesia delivered with a flat-top hand-piece compared to 20% Benzocaine topical anesthetic gel, sixty healthy patients were randomly allocated (1:1) to either 20% benzocaine topical gel + placebo laser (T group) or PBM + placebo gel (L group). The 1064-nm Nd:YAG laser was employed and is associated with a novel flat-top hand piece. The applied operational parameters were 0.5 W, 10 Hz, 100 µs pulse width, and 30 J/cm^2 for one-minute single application time. The enrolled subjects were asked to assess pain intensity at the time of anesthetic injection with a Visual Analog Scale. Taking into consideration taste, undesirable numbness, and overall satisfaction, the patients were asked to rate their experiences according to a verbal rating scale. Statistical analysis showed no statistically significant difference between the T and L Groups for pain ratings ($p = 0.0596$). The L Group displayed significantly higher ratings than T Group for taste, undesirable numbness, and overall satisfaction ($p < 0.001$). The 1064-nm PBM delivered by flat-top hand piece is effective in inducing mucosal anesthesia, eliminating the adverse side-effects of the conventional topical anesthetic gel.

Keywords: low level laser therapy; LLLT; topical anesthesia; local anesthetic injection; pain; Nd:YAG laser; light therapy

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1. Introduction

The peri-apical local anesthetic injection is a very common key element and effective procedure before any dental intervention, but it may frequently be associated with fear of needles and painful administration [1]. Therefore, several dental topical anesthetic agents are used in an attempt to reduce or eliminate pain perception, fear, or phobia and to increase patients' acceptance and satisfaction [2]. Topical anesthetics act on the peripheral nerves and reduce the sensation of pain at the site of application. However, adverse events such as allergy and local anesthetic systemic toxicity (LAST) have been associated with their usage [3], as well as side effects through overuse or overdose [4]. Frequently, they might trigger bad taste, a feeling of numbness in the mouth that may extend to the throat, which incites subjective repulsion and dissatisfaction and can lead to trouble swallowing or even choking [5]. Additionally, pharmacological interventions are associated with increased costs [6]. Traditional common topical anesthetics used in dentistry and

approved by Food and Drug Administration (FDA) contain lidocaine or benzocaine as active ingredients and are used in the form of solutions, creams, gels, and sprays [1,7]. Those agents have been thoroughly investigated, but with contrasting results [3]. It is also for this reason that alternative pretreatment of the site of injection to reduce side effects or costs such as phytotherapy [8], acupuncture and acupressure [9], transcutaneous electric nerve stimulation [10], tissue vibration [11], cryoanesthesia [12], and hypnosis [13] are described despite the lack of a univocal conclusion.

Recently, the effects of light in the visible and near-infrared range on trigeminal nerve pain and regeneration [14], facial nerve inflammation in Bell's Palsy [15], chronic facial myalgia [16], dentinal hypersensitivity [17], and sensory digression in the inferior alveolar nerve [18] were thoroughly reviewed. Moreover, the possible topical anesthetic effect of light therapy was investigated with conflicting conclusions [19,20]. This medical therapy was initially described as Low-Level Laser Therapy (LLLT) but recently the term photobiomodulation (PBM) was preferred. The PBM is a non-ionizing and non-thermal process caused by the absorption of photonic energy in specific endogenous cellular photoacceptors, and that elicits biological effects [21,22]. Basically, modulation of the mitochondria cell metabolism [14,22,23], the membrane depolarization [24], the release of neurotransmitters [25], and the ions' channels opening [25,26] can occur through the transformation of physical energy into chemical energy [22], as well as modification of the vibrational nature of water molecules [27].

The 1064-nm Nd:YAG (neodymium-doped yttrium aluminum garnet) laser wavelength has more recently been adapted to deliver pulpal analgesia in dentistry [28] and its ability to modulate mitochondria and cell activities was proved in extracted organelles and pre-nervous unicellular models [29,30]. In addition, the Nd:YAG is a laser operating in a pulsed mode, which generates high peak power characterized by deeper penetration and polarization's preservation to various degrees in pigmented tissues [31].

Therefore, to investigate the anesthetic effectiveness of 1064-nm Nd:YAG PBM irradiated through a novel hand-piece with a flat-top beam profile, a randomized, double-blind, controlled trial was conducted according to the CONSORT guideline.

The predictor variable was the ability of 1064-nm PBM delivered through flat-top skills to modulate cell metabolism and homeostasis [29,30]. The primary endpoint was the induced mucosal anesthesia. The secondary endpoint was major effectiveness and/or patient satisfaction of PBM vs. 20% benzocaine.

2. Materials and Methods

2.1. Study Design and Participants

Our double-blind Randomized Clinical Trial (RCT) has followed the CONSORT guidelines (Figure S1) and was approved by Saint Joseph University Ethics Committee and Review Board (reference no.: USJ-2021-119, Beirut Lebanon). The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local laws. All patients provided written informed consent.

Eligible patients were females or males who needed a simple routine dental treatment with buccal infiltration to anesthetize the anterior superior alveolar nerves (anterior maxillary region from canine to canine). Patients were excluded if they presented acute swelling, infection at the site of injection, or any neurological or psychological disorders, if they were on anti-inflammatory medications, any analgesics, any antidepressant, or antiepileptic medications three months before the enrolment, and if they had a history of known allergy to any anesthetic compositions. Pregnant or lactating women were also excluded. A full medical history of each subject was obtained, and a thorough oral examination was undertaken before participation in the study.

2.2. Randomisation and Masking

Patients were randomly allocated (1:1) to either 20% benzocaine topical gel + placebo laser (T group) or photobiomodulation + placebo gel (L group). Randomization was based

on a random-sequence software program (www.random.org/sequences on 1 October 2021), which generates randomized sequences. The patients who were assigned an odd number were added to the T group, while patients who were assigned an even number received the L group treatment.

The placebo gel was similar-looking [32] without 20% benzocaine and cannot influence the nociception. According to our previous study [33], the laser placebo consists of photobiomodulation therapy irradiation with the device switched on 0 W. A 532-nm visible green-light guide (negligible power) with the laser device switched to silent mode was used during all the irradiation in order to keep the therapies blinded [33]. Therefore, patients and study team members responsible for the administration of the treatment were masked in treatment allocation. Two experienced clinicians other than the operators involved in irradiation therapies, which were calibrated to 100% intraexaminer agreement for all the evaluated criteria before the study, performed an independent assessment of the experimental purposes. The two examiners were blinded to the two experimental groups. The investigator responsible for statistical data analysis was also masked to treatment assignment. An anonymously numbered questionnaire was used to gather patients' screening information.

2.3. Procedure

2.3.1. 20% Benzocaine Topical Gel + Placebo Laser (T Group)

The topical 20% benzocaine gel (GumNumbTM, CROSSTEX, Maumee, OH, USA) was used due to its potent effectiveness [34]. It was applied to the corresponding mucosal area, using a sterile cotton pellet according to the manufacturer's instructions. The two grams of the gel used for each application were measured with a dosing spoon. Next, the gel was rubbed with moderate pressure over the mucosa for 30 s. Irradiation through the placebo laser (0 W, 0 mJ, 0 Hz, 0 µs pulse width, 0 J/cm^2) and the flat-top hand-piece was performed for 60 s with the gel left in-situ (90 s; the total gel in-situ time) [34]. The patient was asked to keep his mouth open in an attempt to reduce the risk of gel diffusion within the oral cavity and to perform the PBM therapy irradiation. At the end of the treatment, an injection of local anesthetic was slowly administered in respect of the procedure (Figure 1). Subsequently, the patients were asked to rinse their mouths thoroughly in order to wash out the remnants of the anesthetic gel.

2.3.2. Photobiomodulation + Placebo Gel (L Group)

The similar-looking placebo gel was applied according to the topical 20% benzocaine gel administration previously described. The laser device employed in the treatment is a solid-state free-running-pulse Nd:YAG (1064-nm) laser (LightWalker ATS®; Fotona, Ljubljana, Slovenia). The aiming beam is of a low-power visible green semiconductor diode laser (532-nm, power < 1 mW) and is transmitted coaxially along with the optical fiber.

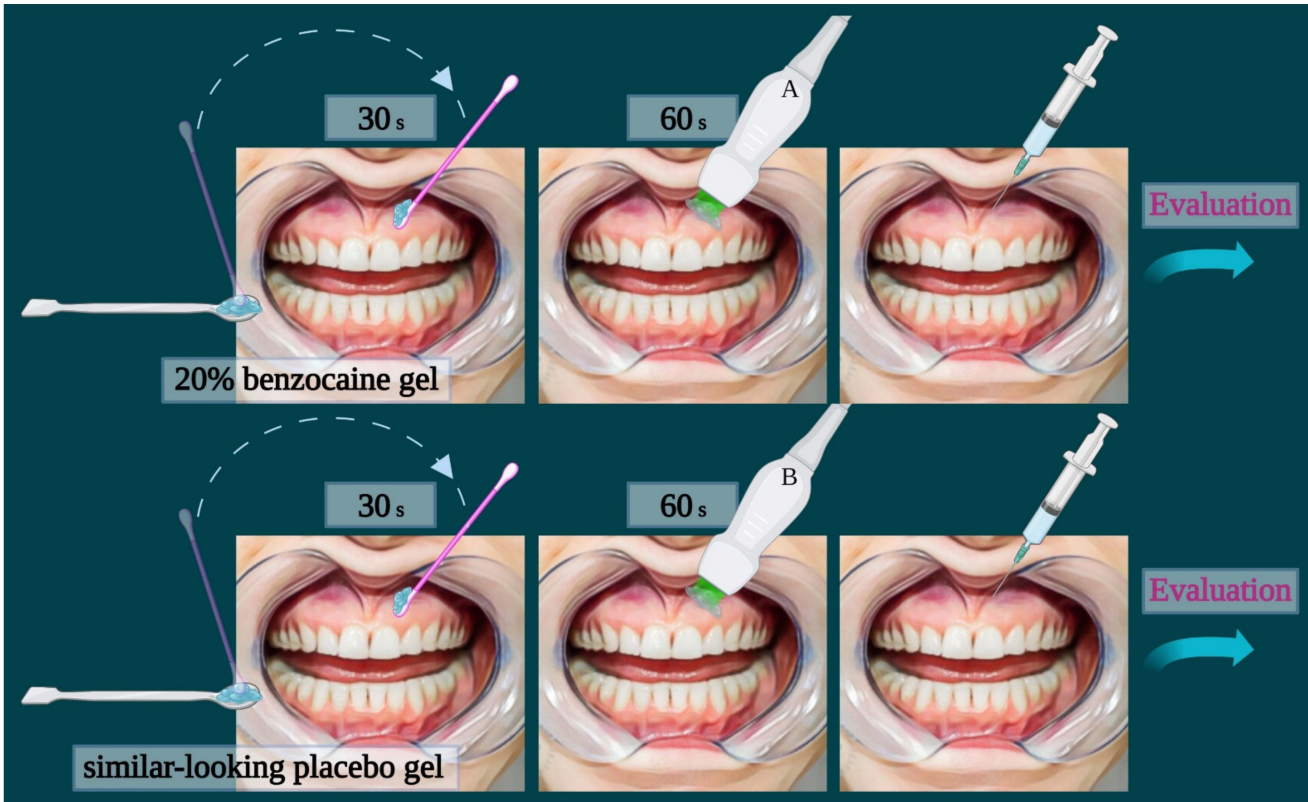
According to our data on the flat-top hand-piece characterization [35], the probe showed the following skills: (1) emits an energy beam covering an area of 1 cm^2, (2) provides the same power density over any tip-to-tissue distance from contact up to around one meter, (3) supplies a uniform distribution of the energy density to the target.

In previous studies, we showed that a laser PBM protocol of 1064-nm with the parameters showed in Figure 1, irradiated through a flat-top hand-piece (Genova®, Fotona, Ljubljana, Slovenia) was able to stimulate mitochondria energetic metabolism and cell proliferation, without inducing adverse effect [29,30]. Therefore, in our work, the same protocol was followed, and the photonic energy was delivered through the Genova® hand-piece, which was kept stationary in non-contact with the buccal mucosa, at an exposure time of 60 s (Figure 1). At the end of the treatment, an injection of local anesthetic was slowly administered in respect of the procedure.

The precision of the laser therapy parameter was secured by the Pronto-250 power meter (Gentec Electro-Optics, Inc. Québec, QC, Canada).

Adverse events due to a possible undesirable thermal effect were avoided by monitoring the irradiation with a thermal camera FLIR ONE Pro-iOS (FLIR Systems, Inc. designs, Portland, OR, USA) (dynamic range: −20 °C/+400 °C; resolution 0.1 °C).

All laser safety measurements were respected in accordance with the American National Standards Institute (ANSI) guideline [36].



Laser Manufacturer	*Fotona*	Model	*LightWalker ATS*
Type	*Nd:YAG*	Probe	*flat-top hand-piece*
(A) 20% benzocaine topical gel + placebo laser (T group)			
Light guide: *532*-nm **- Power:** *<1* mW			
Wavelength (nm)	*0*		
Pulse Width	*0*	Pulse repetition rate	*0*
Average power	*0*	Average power density	*0*
Average energy density	*0*	Spot area at tissue	*1.00* cm^2
Peak power density	*0*	Peak power	*0*
(B) photobiomodulation + placebo gel (L group)			
Light guide: *532*-nm **- Power:** *<1* mW			
Wavelength (nm)	*1064*		
Pulse Width	*100* µs	Frequency	*10* Hz
Average power	*0.5* W	Average power density	*0.5* W/ cm^2
Average energy density	*30* J/cm^2	circular spot area at tissue	*1.00* cm^2
Peak power density	*500* W/cm^2	Peak power	*500* W

Figure 1. Illustration of the anesthetic procedures—Table of the adjustable and calculated laser parameters.

2.3.3. Local Anesthetic Injection Protocol

The same therapeutical protocol and pharmacological approach were used for all the subjects. The site of the needle administration of local anesthesia was kept dry with sterile gauze or cotton rolls and by using a saliva ejector as needed [37]. At the end of the treatments of topical anesthetic application, 2.2 mL of 4% articaine with 1:100,000 epinephrine injection solution was administered in situ. The same anesthetic agent (Septanest™ 1:100,000 epinephrine, Septodont, Saint-Maure-des-Fossés Cedex, France) and the same needle (Septoject Evolution™, 30G short, double-bevel, Septodont, Saint-Maure-des-Fossés Cedex, France) were used for every local anesthetic administration. In our study, we followed the anesthetic technique advocated by Malamed and collaborators [38]. The injection needle was inserted into the height of the mucobuccal fold 3 to 5 mm deep into the labial mucosa. Care was taken to prevent the needle from coming in contact with the bone and the local anesthetic solution was deposited over 20 s [39].

2.4. Evaluation

After completing the local anesthetic injection, the patients were asked to provide their responses.

2.4.1. Visual Analog Scale (VAS)

The primary outcome was pain intensity, in which scores were recorded by all the recruited patients for both groups, using the VAS [40] at the time of local anesthetic injection was administered buccally. All the subjects were made familiar with the VAS before the commencement of the treatment.

The VAS delineates six "smile" graphics. The patients were requested to choose one of these that best represents the level of discomfort or pain experienced. The scores 0 (no pain), 2 (mild), 4 (moderate), 6 (severe), 8 (very severe), and 10 (unbearable) were assigned to each face consecutively from no pain to more painful faces (Figure 2).

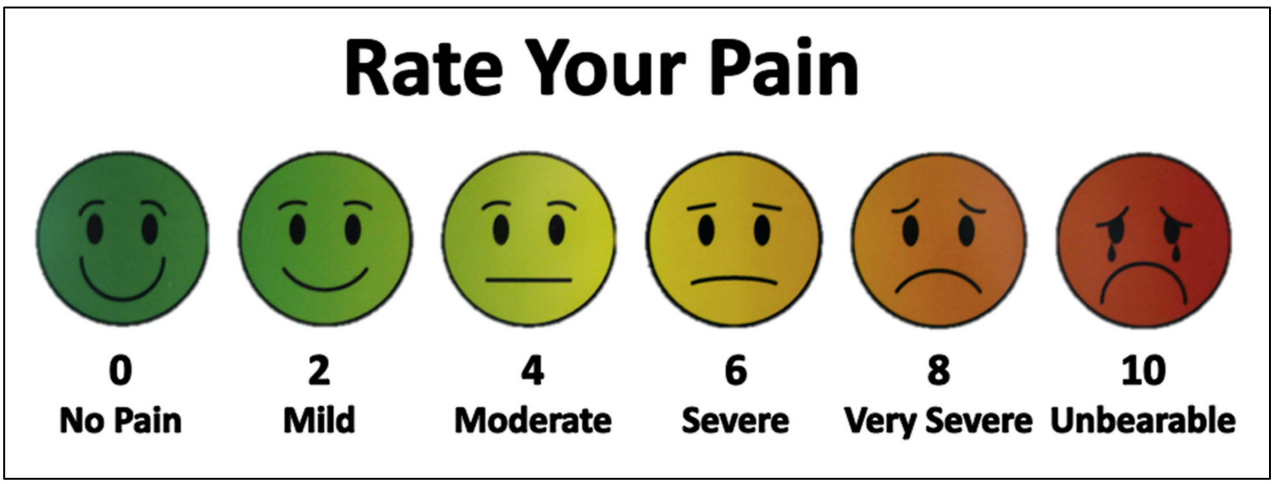


Figure 2. Visual Analog Scale delineating six smile graphics.

2.4.2. Verbal Rating Scale (VRS)

In terms of taste, undesirable numbness, and overall satisfaction, the patients were asked to rate their experiences according to the verbal rating scale illustrated in Table 1:

Table 1. The verbal rating scale and its descriptions for the following variables: taste, undesirable numbness, and overall satisfaction, where the participants rate their scores.

Score	Taste	Undesirable Numbness	Overall Satisfaction
1	Awful	Awful	Awful
2	Very bad	Very severe	Very bad
3	Bad	Severe	Bad
4	Moderate	Moderate	Good
5	Mild	Mild	Very good
6	No taste	No numbness	Excellent

2.5. Outcomes

In accordance with our previous works [29,30,35], the predictor variable was the 1064-nm PBM ability to interact with cellular target involved in the energetic metabolic metabolism and the novel hand-piece with a flat-top beam profile skill. The primary endpoint was the induced mucosal anesthesia. The secondary endpoint was major effectiveness and/or patient satisfaction of PBM vs. 20% benzocaine.

2.6. Data Analysis

The measures collected were statistically analyzed while considering the mean and standard deviation of the measured data and the statistical power of the sample size. Linear models were used to assess the data and calculations were performed using a script in the programming language R. First, the data were evaluated to check the normality distribution by using the Kolmogorov–Smirnov test and the reliability by calculating the Cronbach's coefficient ($\alpha < 0.05$). Second, the data was then analyzed using a one-way Analysis of variance (ANOVA) with an intra-group comparison performed by Tukey's post hoc test. Furthermore, the data were also analyzed using binomial linear regression and Pearson's chi-square test. The level of significance was established at 95%. The value $p < 0.05$ was accepted as the significance level of the tests.

The sample size was calculated by G*Power Statistical Power Analyses Software version 3.1.9.7. [41]. The power analysis showed that to have a power of 80% with an effect size of (d = 0.8) and α error of 0.05, a sample size of 52 patients (26 patients per group) could be sufficient.

3. Results

3.1. Participants and Randomization

Between 1 October 2021 and 1 February 2022, 70 patients were screened for the study; eight patients were deemed ineligible and two patients declined to participate (Figure S1). Sixty patients were randomly assigned and consisted of the intention-to-treat population. Thirty of them were allocated to 20% benzocaine topical gel + placebo laser (T group) and 30 were allocated to the photobiomodulation + placebo gel (L group). All 60 patients received the randomly assigned treatment.

The T group was made up of Caucasians (55.17% females and 44.82% males) with a mean age ± standard deviation = 42.27 ± 14.83. The L group was composed of Caucasians (53.33% females and 46.67% males) with a mean age ± standard deviation = 45.4 ± 15.84. No statistical difference was observed concerning the age of the two groups ($p > 0.05$).

A full medical history of each subject was obtained, and a thorough oral examination was done prior to participation in the study. Accordingly, and following the established inclusion/exclusion criteria, the 60 recruited patients were judged to be in good general health and able to self-complete the VAS and the verbal questionnaire for evaluation.

All the sixty enrolled patients completed the treatments successfully. No adverse effects were reported.

3.2. Primary Variable

Pain Intensity Evaluation

For the pain ratings evaluated by participants, a one-way ANOVA with post-hoc Tukey HSD analysis was conducted. There was no significant difference between the T and L Groups *(F(1,58) = 3.691, p = 0.0596)* and average rating given by patients was *M = 1.3, (SD = 0.961)* with rating of 1 representing "no pain felt", as shown in Figure 3. Further analysis was conducted using binomial linear regression and Pearson's chi-square test. No significance was found with $\chi^2(1) = 3.64$, $p > 0.05$.

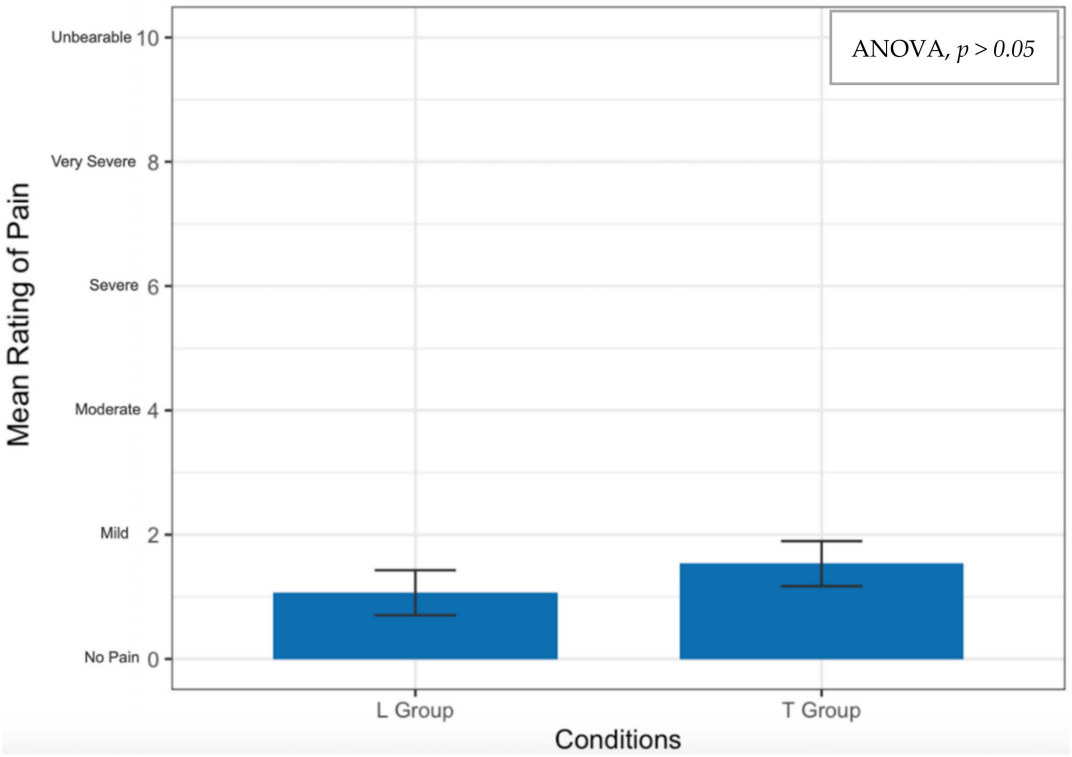


Figure 3. Illustrates the mean ratings of pain with associated standard deviation for both groups (L and T), where 0 represents no pain and 10 represents unbearable pain. Abbreviations: T Group: 20% benzocaine topical gel + placebo laser; L Group: photobiomodulation + placebo gel.

3.3. Secondary Variable

3.3.1. Taste Evaluation

Taste ratings were evaluated by participants, and a one-way ANOVA with posthoc Tukey HSD analysis was conducted. L Group had significantly higher ratings than T Group with *F(1,58) = 546.5, p < 0.001* with the average rating given by patients being *M = 4.166, (SD = 1.88)* with a rating of 6 representing no taste felt and 1 representing "awful", as shown in Figure 4. L Group participants rated no taste *M = 6, (SD = 0)*; however, T Group participants rated taste with *M = 3.7, (SD = 0.54)*.

3.3.2. Evaluation of Undesirable Numbness of the Mouth

Numbness ratings were evaluated by participants, where the L group had significantly higher ratings than the T group with *F(1,58) = 525.1, p < 0.001*, using the one-way ANOVA analysis. The average rating given by patients was *M = 5.2, (SD = 0.91)* with a rating of 6 representing "no numbness felt" and 1 representing "awful", as shown in Figure 5. The L group's participants rated "no numbness" *(M = 6, SD = 0)*; however, T group participants rated numbness as *M = 4.4, (SD = 0.62)*.

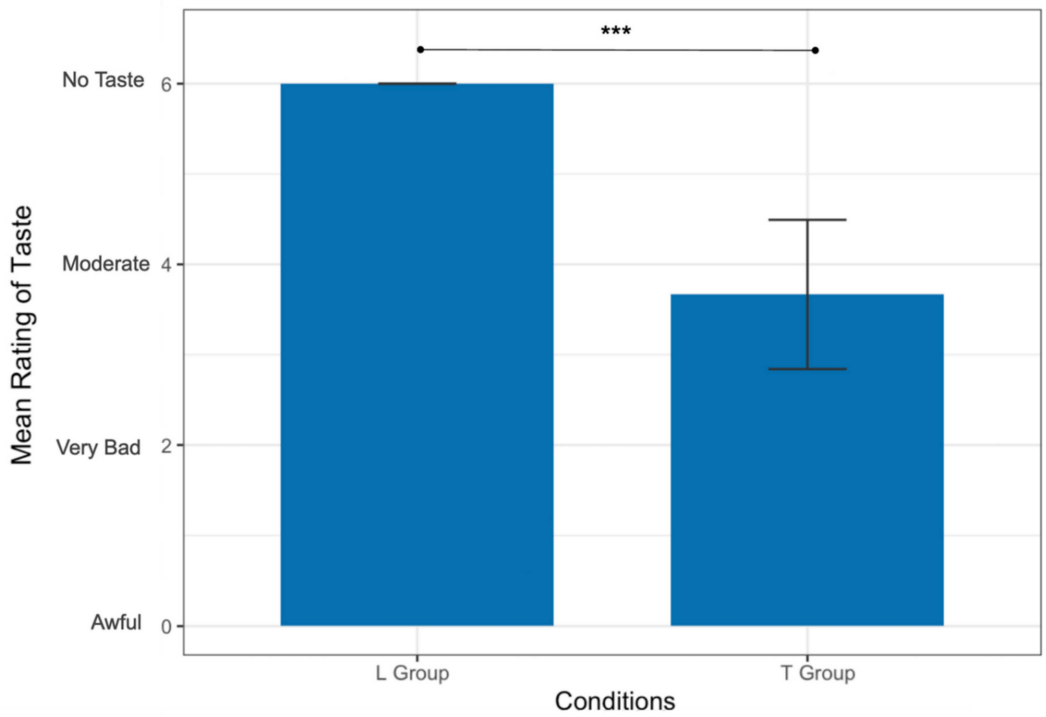


Figure 4. Illustrates the mean ratings of taste with associated standard deviation for both groups where 0 represents awful and 6 represents no taste perception. Abbreviations: T Group: 20% benzocaine topical gel + placebo laser; L Group: photobiomodulation + placebo gel. [***] represents significance at the $p < 0.001$ level.

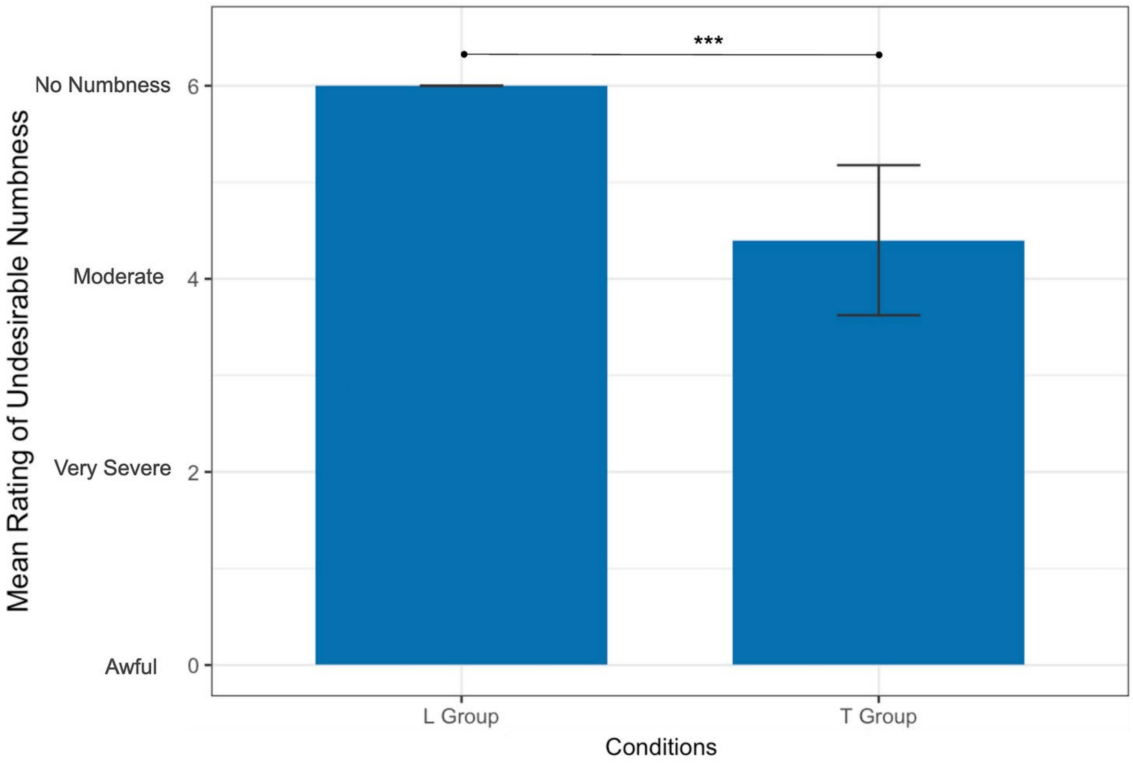


Figure 5. Illustrating the mean ratings of undesirable numbness with associated standard deviation for both groups (L and T), where 0 represents awful and 6 represents no undesirable numbness. Abbreviations: T Group: 20% benzocaine topical gel + placebo laser; L Group: photobiomodulation + placebo gel. [***] represents significance at the $p < 0.001$ level.

3.3.3. Patients' Overall Satisfaction

The satisfaction ratings were evaluated by participants. The L group had significantly higher ratings than the T group with $F(1,58) = 38.77$, $p < 0.001$ using the one-way ANOVA analysis. The average rating given by patients was $M = 4.98$, $(SD = 0.77)$, with a rating of 6 for "Excellent" satisfaction and 1 for "Awful" satisfaction, as shown in Figure 6. The L group's participants rated overall satisfaction as $M = 5.46$, $(SD = 0.57)$ and the T group's participants rated the overall satisfaction as $M = 4.5$, $(SD = 0.62)$.

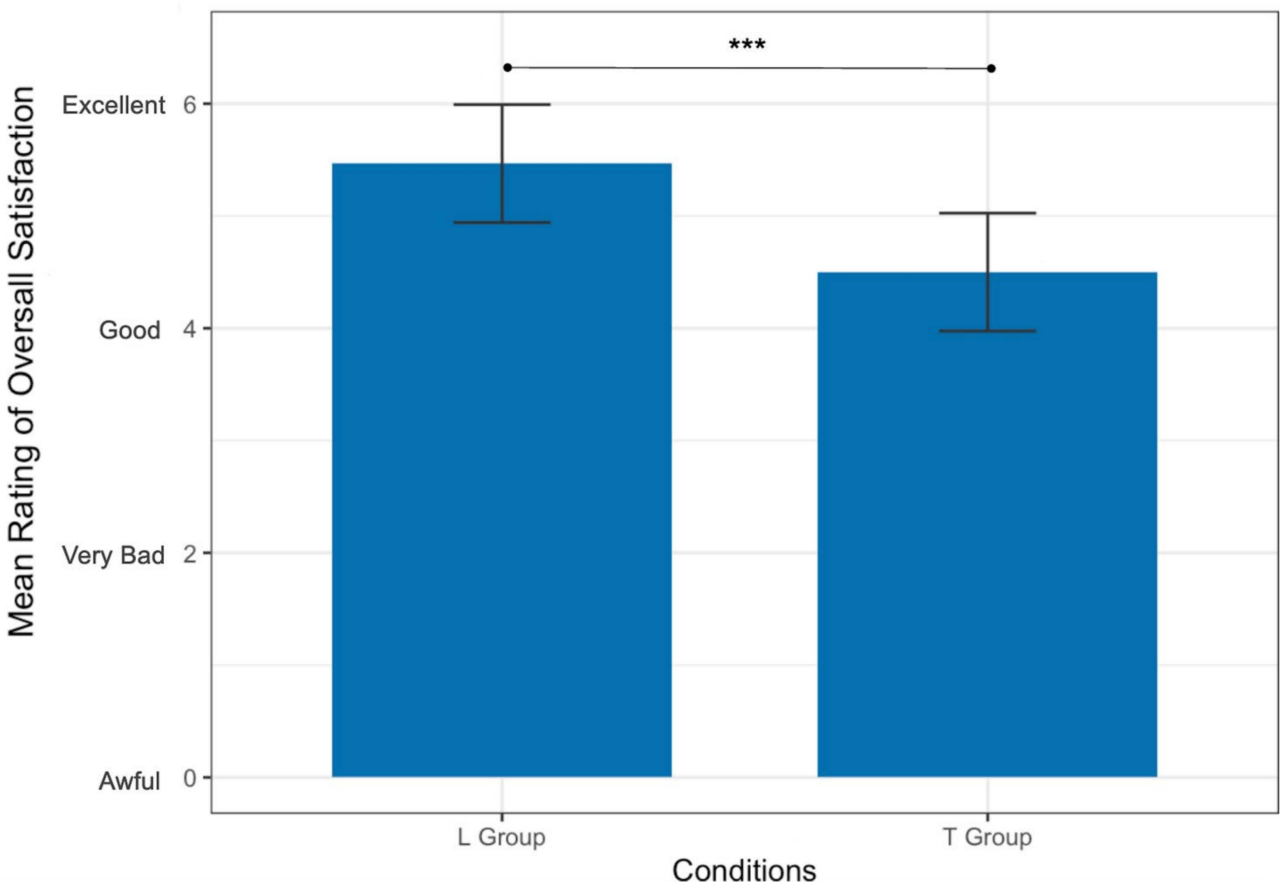


Figure 6. Illustrating the mean ratings of overall satisfaction with associated standard deviation for both groups (L and T), where 0 represents awful and 6 represents excellent. Abbreviations: T Group: 20% benzocaine topical gel + placebo laser; L Group: photobiomodulation + placebo gel. [***] represents significance at the $p < 0.001$ level.

4. Discussion

Photobiomodulation therapy was effective in the mucosal anesthetic experience. Indeed, our study showed that subjects in the L group (photobiomodulation + placebo gel) have reported similar pain intensity that the T group (20% benzocaine topical gel + placebo laser), at the time of the local anesthesia (LA) injection. This complies with the primary endpoint and demonstrates the similar efficacy of 1064-nm PBM in inducing mucosal anesthesia and subsequently a decrease in pain intensity when compared to 20% benzocaine topical gel. Moreover, the secondary endpoint correlated to the discomfort experienced was significantly reached in the L group. Indeed, our data showed that the subjects in the T group have reported more discomfort and less overall satisfaction, compared to the L group; neither group reported adverse effects. These clinical results comply with our previous in vitro and like vivo evidence [29,30].

Indeed, the parameter irradiated in our work, such as 1064-nm Nd:YAG, 0.5 W, 10 Hz, 100 µs pulse duration, 60 s exposure time, 30 J/cm^2, spot size area 1 cm^2, induced positive PBM effects on the unicellular pre-nervous model *Paramecium primaurelia* through

modulation in oxygen consumption, endogenous ATP synthesis, and fission rate rhythm, while heat shock proteins (HSP) expression was not affected [30]. Additionally, in bovine liver extracted mitochondria, the same parameters were able to modulate the aerobic metabolism through interaction with the cytochromes of the respiratory chain complexes, hence an increase in ATP production was observed [29]. Of note, both models have previously been effective in the prediction of PBM therapy's effect on vertebrates and humans. In fact, 808-nm, 1 W, continuous mode of irradiation (CW) for 60 s, 60 J/cm^2, spot size area 1 cm^2, affected *P. primaurelia* [42] and isolated bovine mitochondria [43], but also reduced inflammation in the murine model and humans [15,44] and pain in patients affected by major aphthae [33]. Similarly, 980-nm was able to modulate the Paramecium and the mitochondria [45,46] as well as preserve the socket bone of dogs [47]. Therefore, PBM through near-infrared light exploits the ability of certain molecules by being both photoacceptive and capable of regulating conserved cellular pathways. In addition, the restorative effects of PBM appear to be a byproduct, which was conserved in evolution [22].

Concerning the effect of near-infrared on nociception, Chow and collaborators [48] carefully reviewed the inhibitory effects of laser irradiation on peripheral mammalian nerves. They showed that the slowing in the conduction velocity and the decreasing in action potential amplitudes would reflect on the inhibition of electrophysiological activity. To support our data, Wesselmann and collaborators demonstrated the effect of Q-switched Nd:YAG 1064-nm irradiated through increasing pulse energies ranging from 10 to 100 mJ/pulse for 5 min each on C fiber, which is involved in nociception and pain of peroneal tibial and saphenous nerve models. The nociceptor activity was suppressed [49]. Additionally, Wesselmann and collaborators showed ultrastructural changes of axonal organelles in nonmyelinated fibers after irradiation with 1064-nm Q-switched Nd:YAG laser (70 mJ, 10 Hz, 8 ns pulse duration, 5 min irradiation). The conduction velocity and horseradish peroxidase transport properties of fibers, which may be seen as a common mechanism of analgesic effect, were affected [50]. Animal studies conducted by Orchardson and collaborators highlighted the increase in the pain threshold of teeth [51,52] as a consequence of the 1064-nm pulsed Nd:YAG laser action on reversible intra-dental nerve conduction. Basically, the results showed that laser irradiation with an average power < 1.5 W for 60 s (30–150 mJ, 10–20 Hz, 150 µs pulse duration) has produced a significant reversible neuronal activity blockage. This evidence can therefore explain and support the effect of 1064-nm photobiomodulation on our patients.

Concerning the literature, the comparison of the photobiomodulation analgesic effects is not straightforward. According to Karu [53], PBM in some cases mimics the drugs' effects. However, the mimetic action of PBM is a result of a complex equilibrium among wavelengths, powers, times, irradiation modes, fluences, energies, and irradiated area sizes, which allow experiencing PBM effects, but limit the generalization of the therapy.

The comparison between the use of PBM at low power parameters and 20% benzocaine topical application to induce mucosal anesthesia before a dental local administration in adults has been reported in a limited number of studies. Moreover, a wide variety of diode laser wavelengths characterized by a Gaussian beam profile delivery were investigated and the obtained results were inconsistent due to a lack of standardization in the applied laser protocols and techniques [54]. Sattayut and collaborators [55] investigated the use of 790-nm diode laser, 0.3 W in CW (continuous wave mode) in contact for 2 min. Similar to our investigation, they found that although the laser group's pain score was better, there were no statistically significant differences when compared to the 20% benzocaine group. On the contrary, Ghaderi and collaborators [19] concluded that laser therapy did not reduce pain perception during the insertion of a needle. Similar results were obtained using an 810-nm diode laser (198 mW, CW, 30 s, 2 sessions) on pre-injection sites in patients scheduled for third molar removal [56].

Jagtap and collaborators [20] investigated a 660-nm diode laser with an output power of 60 mW, whereby the laser therapy statistically reduced pain perception when compared to the laser sham group.

Nevertheless, in another randomized clinical trial, PBM-t using 980-nm diode laser (0.3 W, CW, 20 s) decreased pain level during local anesthesia injection with no statistically significant differences from the placebo group. However, the severity of pain in the laser group was significantly lower than in the control group where no pre-treatment was done [57]. Amrutavarshini and collaborators reported that PBM-t (810-nm diode laser, 0.3 W, gated mode, 2 mm tip-to-tissue, 1 min irradiation time) was statistically less effective than topical 20% Benzocaine anesthetic gel or precooling with ice on children [58]. This is in contrast with our results and can be explained by the difference in age groups investigated, wavelengths, and mostly the difference in laser operational parameters. Amrutavarshini and co-workers used an 810-nm diode laser with a Gaussian profile delivery mode at an output power of 0.3 W provided in a gated mode and that may have reduced the amount of power delivered to the tissue. In addition, the laser technique was not fully described. Moreover, measurement of pain is a challenging task, especially while working with children [59].

On the contrary, a different laser protocol addressing a recent triple-blind randomized clinical trial on children reported no statistically significant difference between PBM-t with 808 nm diode laser (250 mW, CW, 65 s irradiation time, in perpendicular tissue contact) and benzocaine topical gel. They concluded that PBMT can be an effective nonpharmacological technique for controlling injection pain [60]. Similar findings were reported by Uçar and collaborators using an 810-nm diode laser (0.3 W, CW, 20 s irradiation) [61]. A PBM-t with 915-nm diode laser wavelength (1.5 W, 60% duty-cycle, 15 Khz, 40 s irradiation) was used to assess pain reduction during maxillary incisors' local infiltration in adults and showed a statistically higher numerical rating scale for pain in the sham laser group. It was found that PBM-t had a significant effect on pain reduction during either needle penetration or injection [62]. Very restricted clinical trials investigated PBM-t using our 1064-nm Nd:YAG laser wavelength on pain reduction during local anesthesia. The findings of a clinical trial conducted by Chan and collaborators [28] reported no side effects for the Nd:YAG laser group (15 Hz, 60–87 mJ, 150 µs pulse duration, focused scanning motion for 240 s) in terms of unpleasant taste, numbness, and mucosal irritation. These findings are in accordance with our results and show that the PBM-t with Nd:YAG laser wavelength is a safe and satisfactory maneuver.

Therefore, a wide range of wavelengths and parameters can induce an analgesia experience. Wavelengths of the visible and near-infrared spectrum showed different cellular targets [21]. However, the main role of the mitochondria seems conserved and affected through a wide range of frequencies from visible to near-infrared [23,24,29,35,43,46]. Consequently, at the base of all the effects, modulation of ATP concentration could influence the action of Na^+, K^+-ATPase and its role in membrane depolarization that supports the antinociceptive effect of drugs [63] as well as neurotransmitter release [25].

Our study has limitations because the employment of VAS solely and rating scales could influence bias. In addition, only one maxillary area was investigated, and future work should include other jaw regions. However, the double-blind randomized clinical trial setup and the sample size, which allowed an adequate study power, were both strengths. Furthermore, it is important to stress that the therapy parameters used in our work were characterized by reliable preclinical experimental models [30] and our results are coherent with the 1064-nm PBM effect on nerve fibers. Hence, PBM therapy using low-power pulsed near-infrared Nd:YAG laser can be considered as an alternative non-invasive, non-thermal, free injection-related anxiety, with no adverse side effects, and is effective in inducing pre-operative localized anesthesia [64,65].

5. Conclusions

In summary, our randomized, double-blind trial supports the effectiveness of our 1064-nm photobiomodulation (0.5 W, 50 mJ, 10 Hz, 100 µs pulse width, 30 J/cm^2) as a topical anesthetic. The effect appears similar to 20% Benzocaine, which is known to reduce the pain intensity before LA injection. However, with PBM therapy, patients do not experience

undesirable effects in terms of unpleasant taste and numbness of the entire mouth and are not exposed to allergic reactions or side effects as with chemicals. Lastly, the employment of the novel flat-top delivery technology, which in previous works improved the consistency of the PBM effect with respect to standard probes, supports the reproducibility and standardization of the therapy which could appear as operator-dependent.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/photonics9080519/s1, Figure S1: CONSORT flow chart illustrating the participants' enrolment, groups and interventions.

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