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Impact of Single-Session Intraoral and Extraoral Photobiomodulation on Pain Control after Extraction of Impacted Mandibular Third Molar: A Pilot Study

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Abstract: This study aims to evaluate the impact of a single session of intraoral and extraoral photobiomodulation (PBM) on controlling pain and improving a patient's daily activities following surgical extraction of the impacted mandibular third molar, using combined three wavelengths: "445 nm, 660 nm, and 970 nm". A pilot study was conducted on 22 patients undergoing extraction of an impacted mandibular third molar. The patients were randomly divided into two groups: (1) The Test Group consisted of patients subjected to immediate postoperative PBM. The extraoral PBM parameters were power = 550 mW and spot area = 5 cm^2, while the intraoral parameters were power = 200 mW and spot area = 2 cm^2. (2) The Control Group consisted of the patients not subjected to PBM. For all the patients, the pain was evaluated via a Numeric Rating Scale (NRS) on day 0, day 1, day 3, and day 7 after surgical intervention. The patient's daily activities were evaluated on day 7 via a custom-made questionnaire. A statistically significant difference was observed between groups in the pain NRS scores on day 0 ($p = 0.022$), day 1 ($p = 0.047$), and day 7 ($p = 0.028$). No significant difference was found on day 3 ($p = 0.153$). A marginal statistical significance was observed with the number of painkillers taken ($p = 0.054$). No significant difference was observed with the questionnaire score ($p = 0.206$). This pilot study showed a significant reduction in postoperative pain on days 0, 1, and 7 with a single session of intraoral and extraoral PBM. However, the number of painkillers taken and the scores of the daily activities questionnaire did not show statistical significance despite the observed better results in patients subjected to PBM.

Keywords: diode laser; photobiomodulation; pain; surgical extraction; mandibular third molar

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1. Introduction

The surgical extraction of the mandibular third molar is one of the most frequent oral surgical procedures performed in dental clinics. Several postoperative complications have been reported including pain, edema, trismus, and/or functional limitation. These complications may eventually have an impact on the patient's quality of life [1]. The postoperative patient discomfort might be due to triggering an inflammatory response [2].

Pain represents the major postoperative problem, as it may affect 20–40% of patients. The most intense pain is predicted in the first 12 h after surgery and may endure up to between the third and fifth day after surgery at a lower intensity [3]. The use of anti-inflammatory agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, has been shown to be efficient in the management of these postoperative complications in general and pain in particular [2,4]. However, there are many reported side effects of the use of these drugs, such as gastrointestinal irritation, allergic reactions,

or hemorrhagic complications. In addition, these drugs should be avoided in certain conditions for some patients [5].

Several modifications and improvements in surgical procedures have been proposed as a trial to decrease surgical trauma and, eventually, postoperative discomfort, such as the use of piezosurgery, surgical closure techniques with/without the placement of a drain, cryotherapy, the use of platelet-rich fibrin, and photobiomodulation (PBM) [6–11].

PBM is the application of non-ionizing forms of light by utilizing the impact of light energy on living cells for therapeutic purposes. This application may modulate, restore, and stimulate physiological processes, which may eventually lead to the repair of damages caused by injuries or diseases [12]. PBM can induce several physiological pathways, resulting in anti-inflammatory, analgesic, and bio-modulatory effects. Therefore, PBM has been proposed as an adjunctive modality in the management of many medical and dental conditions, such as oral mucositis, oral lichen planus, medication-related osteonecrosis of the jaw, and temporomandibular joint disorders [13–17].

PBM has been widely investigated as an adjunctive modality to the surgical procedure of the extraction of the impacted third molar [11,18,19]. Several meta-analyses and systematic reviews have been conducted in recent years to evaluate the effectiveness of the PBM and determine the best effective protocols [20–24]. In the literature, it appears that the level of the effectiveness of PBM has grown through the years with the performance of studies, as Brignardello-Petersen et al. in 2012 and then Dawdy et al. in 2017 did not observe any positive effect of PBM with third molar surgery [20,21]. In 2021, Domah et al. observed, by adding the new studies to the previous systematic metanalyses, the effectiveness of PBM for swelling but not for pain and trismus [22]. In the same year (2021), Duarte de Oliveira et al. reported in their meta-analysis the effectiveness of PBM for the reduction in pain and edema but not for trismus [23].

Recently, Lacerda-Santos et al. reported, in 2023, the effectiveness of PBM for the reduction in all pain, swelling, and trismus. However, they found that PBM's level of evidence still ranges from low to very low in a way meaning that PBM cannot be considered a routine practice with third molar surgery [24]. They recommended using the combined protocols of PBM (intraoral and extraoral) rather than only the intraoral or extraoral protocol [24]. Most of the wavelengths used for PBM in the studies included in these systematic reviews were red and near-infrared wavelengths [20–24]. All of these systematic reviews recommended conducting further studies in order to determine the effective PBM protocols [20–24]. In addition, to the best of our knowledge, there is no study that evaluates PBM application using a combination of different wavelengths.

In view of the abovementioned observations, we decided to evaluate the impact of a single session of intraoral and extraoral PBM on controlling pain and improving a patient's daily activities following the surgical extraction of the impacted mandibular third molar, using a combination of three wavelengths: "445 nm, 660 nm, and 970 nm".

2. Materials and Methods

A single-center pilot study was carried out on patients referred to the department from January to November 2022. All the study procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was approved by the Local Ethical Committee (Prot. n. 775/17, RIF.CE: 4687). This study was registered on the ISRCTN registry (ISRCTN80613224). An informed consent form was signed by each patient prior to their participation in this study.

Patients undergoing the surgical extraction of a partially bony impacted mandibular third molar with class II or III and position B and C according to the Pell and Gregory classification were included in this study [25]. The inclusion criteria were normal healthy patients of both genders, with an age $\geq$ 18 years, no smoking habits, the absence of pericoronitis, and no allergy to anesthetic solutions. The exclusion criteria were patients who refused participation in the study, pregnant or lactating patients, patients who were sub-

jected to anti-inflammatory drugs or antibiotic therapy less than 2 weeks before the surgical intervention, patients with systemic disorders, and patients who did not complete the designed questionnaires in this study. The inclusion and exclusion criteria were established and based on including patients with the same level of difficulty of surgical extraction and excluding patients who have a systemic condition or had/have any history of drug intake (such as anti-inflammatory or antibiotic drugs) that may influence the healing process and, therefore, may influence the results.

Patients fulfilling the inclusion criteria were randomly allocated to two groups: (1) the Test Group (TG) consisted of patients who were subjected to intraoral and extraoral PBM applications immediately after surgical extraction, and (2) the Control Group (CG) consisted of patients who were subjected to only the surgical intervention without PBM application. Opaque and sealed envelopes were prepared, in which "with PBM" or "without PBM" was written. After making a decision regarding the eligibility of the patient and obtaining consent, the allocation of the patient in a group was determined by a professional not involved in this study, who blindly selected the envelope for each patient.

2.1. Surgical Intervention

All the patients in both groups were subjected to a standardized surgical approach by the same operator. An inferior alveolar nerve block, lingual nerve block, and buccal nerve block were performed using 1.8 mL of mepivacaine containing 1:100,000 epinephrine. A mucoperiosteal flap was established using a #15 scalpel (for incision) and mucoperiosteal elevator. A carbide round bur mounted on a straight handpiece was used for osteotomy on the buccal and distal areas. In case of necessity, tooth sectioning was performed using a fissure bur mounted on a low-speed handpiece. Saline irrigation was performed during the osteotomy, the tooth sectioning, and after the extraction of the tooth. Closure of the surgical wound was achieved using a non-absorbable 3-0 silk suture material. To ensure the standardization of the surgical procedures, the patients were considered excluded from this study if the surgical intervention duration exceeded 45 min. A prescription of 500 mg of azithromycin (every 24 h for 3 days), chlorhexidine mouthwash (for 7 days), and 400 mg of ibuprofen (only one time after surgery and then if needed) was given.

2.2. PBM Parameters

The patients in the TG were subjected immediately after the surgical intervention to intraoral and extraoral PBM. The used laser device was K-Laser Blu Dental (Eltech K-Laser, Treviso, Italy). The device can emit, in combination or separately, three wavelengths: 445 (±5) nm, 660 (±5) nm, and 970 (±5) nm. Both extraoral and intraoral PBM applications were conducted using the combination of the three wavelengths.

For the extraoral PBM, the parameters were an energy of 99 J, a peak power of 1.1 W (0.5 W for 445 nm, 0.5 W for 970 nm, and 0.1 W for 660 nm), an average total power of 550 mW, and a frequency of 4 Hz. A defocused handpiece with a 32 mm diameter was used, which guarantees a fixed spot area at 2 cm from the surface. The application duration was 3 min. The laser was applied on the mandibular angle "masseter insertion", keeping the handpiece in contact with the skin without movement (Figure 1).

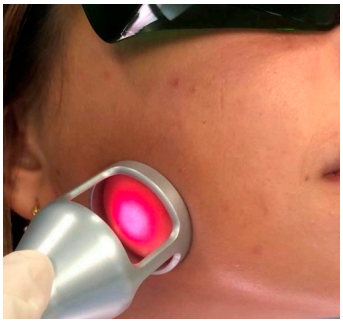

Figure 1. Extraoral photobiomodulation (PBM).

For the intraoral application, PBM was carried out in three phases. Each phase duration was 1 min. The parameters of each phase were an energy of 36 J, a peak power of 0.40 W (0.1 W for 445 nm, 0.2 W for 970 nm, and 0.1 W for 660 nm), an average total power of 200 mW, a frequency of 4 Hz, and a spot area of 2 cm^2. The laser was applied at three different points surrounding the surgical wound (buccal, lingual, and distal) at a distance of ≃1 cm, keeping the handpiece in place without movement (Figure 2). Table 1 shows the parameters used for extraoral and intraoral PBM, as it is recommended in the literature to report the PBM parameters in a table [26].

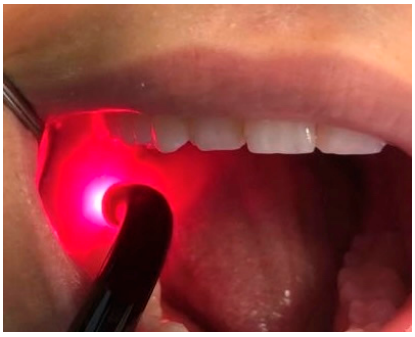

Figure 2. Intraoral photobiomodulation (PBM).

Table 1. Photobiomodulation (PBM) parameters.

Parameter	Extraoral	Intraoral
Manufacturer	Eltech K-Laser	
Model identifier	K-Laser Blu Dental	
Number emitters	Three wavelengths	
Wavelength and bandwidth	445 nm, 660 nm, and 970 nm	
Pulse mode	4 Hz	
Beam spot size at target	~5 cm^2	~2 cm^2
Exposure duration	3 min	3 min (1 min for each point)
Number of points irradiated	One point at the mandibular angle "masseter insertion"	Three points surrounding the surgical wound (buccal, lingual, and distal)
Area irradiated	~5 cm^2	~6 cm^2
Application technique	Without movement in a contact mode	Point by point in a defocused mode
Total irradiation energy	99 J	36 J
Number and frequency of treatment sessions	Single session immediately after surgical intervention	

2.3. Follow-Up Assessment

A custom-made chart was prepared in which there were two sections to be completed by the patients: (1) the Numeric Rating Scale (NRS) and (2) the number of painkillers taken during the 7 days after surgery. The NRS had a length of 10 cm (with a range of 0 for "no pain" and 10 for "worst possible pain") and was designed 4 times to evaluate the postoperative pain on day 0 (6 h after the intervention), day 1, day 3, and day 7 after surgical intervention. This custom-made chart was provided to all the patients immediately after the surgical intervention. In addition, a questionnaire was provided to all the patients to be completed on the seventh postoperative day to evaluate the impact of the surgical intervention on their daily activities. This questionnaire was based on a previously reported questionnaire that evaluated changes in a series of daily activities, including social isolation, nutrition, phonation or speaking, sleep, and physical appearance [27,28]. Figure S1 (Supplementary Materials) shows the used questionnaire after being translated into the Italian language. It consists of 14 questions with 4 possible answers with a score of "not at all (0)", "a little (1)", "quite a lot (2)", or "very much (3)". The total score of this questionnaire ranges from 0 to 42. The lowest total score (0) means the least level of patient discomfort, and the highest total score (42) is the highest level of patient discomfort. The

patients were asked to bring back both the custom-made chart and the questionnaire to the next follow-up meeting.

2.4. Statistical Analysis

All the retrieved data from both groups were registered in an Excel sheet. The statistical analysis was performed using the statistical processing software SPSS (Statistical Package for Social Science, Armonk, NY, USA) for Windows, release 25.0. The dichotomous variables of the two groups (i.e., gender and the side of the extracted tooth) were compared using Fisher's exact test for the verification of the homogeneity of the groups. The mean scores of pain on day 0, day 1, day 3, and day 7; the mean scores of the patient's daily activity questionnaire; and the mean number of painkillers taken were compared using a t-test to evaluate the efficacy of PBM. The two-way ANOVA test was used for determining whether, in addition to the group, time affects the study outcomes. In order to precisely interpret the results of this study with this small sample size, a calculation of the effect size (η2) for the observed effects was performed. The results were considered statistically significant when the p-value ≤ 0.05.

3. Results

A total of 22 patients (12 females and 10 males) were recruited in this study, with 11 patients included in each group (Figure 3). A total of 16 patients (72.7%) were subjected to the surgical extraction of the left lower third molar (tooth no. 3.8), and 6 patients (27.3%) underwent the extraction of the right third molar (tooth no. 4.8).

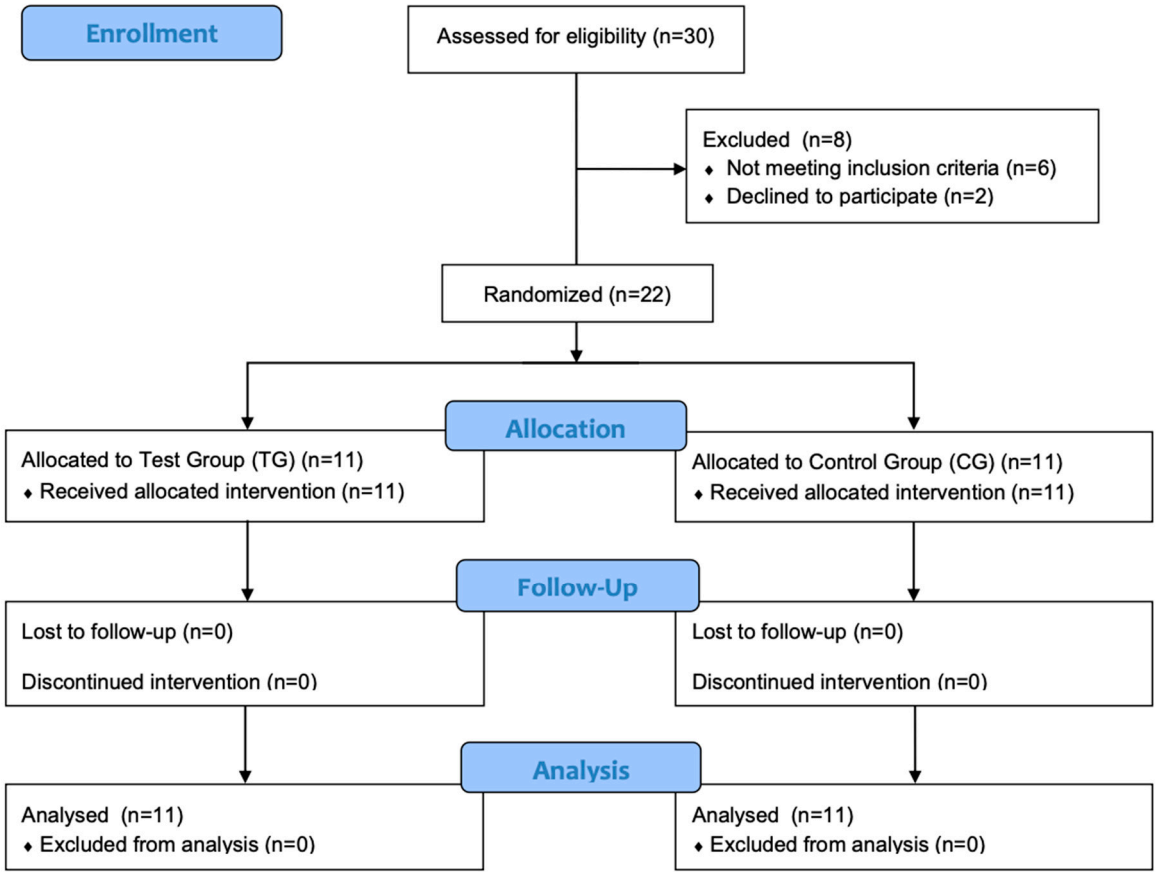

Figure 3. Consort flowchart of the allocation of patients in the Test Group (TG) and Control Group (CG).

In the TG, the patients were distributed as follows: eight females (72.7%) and three males (27.3%). The left lower third molar (tooth no. 3.8) was extracted in 10 patients, and the right lower third molar (tooth no. 4.8) was extracted in 1 patient. In the CG, the patients

were distributed as follows: four females (36.4%) and seven males (63.6%). The left lower third molar was extracted in six patients, and the right lower third molar was extracted in five patients. The surgical intervention durations were similar for both the TG and CG, with a minimum of 15 min, a maximum of 45 min, and an average of 30 min. Table 2 shows the results of the descriptive and statistical analysis.

Table 2. The results of the descriptive and statistical analysis.

Variable	Test Group (TG) $n = 11$	Control Group (CG) $n = 11$	Total $n = 22$	Fisher's Exact Test	*p*-Value
Gender: *n* (%)					
Female	8 (72.73)	4 (36.36)	12 (54.55)	2.93	0.198
Male	3 (27.27)	7 (63.63)	10 (45.45)		
Extracted Tooth: *n* (%)					
4.8	1 (9.09)	5 (45.45)	6 (27.27)	3.67	0.194
3.8	10 (90.91)	6 (54.55)	16 (72.73)		
Numeric Rating Scale (NRS): average (SD [1])				***t*-test**	***p*-value**
Day 0	3.91 (2.34)	6.45 (2.46)	5.18 (2.68)	−2.48	**0.022**
Day 1	3.36 (2.54)	5.55 (2.30)	4.45 (2.61)	−2.11	**0.047**
Day 3	2.59 (2.25)	4.18 (2.75)	3.39 (2.58)	−1.49	0.153
Day 7	0.55 (1.21)	2.73 (2.69)	1.64 (2.32)	−2.45	**0.028**
Patients' Daily Activities Questionnaire: average (SD)	8.27 (7.36)	12.72 (8.57)	10.5 (8.12)	−1.31	0.206
Painkiller Intake: average (SD)	4.36 (3.14)	8.18 (5.34)	6.27 (4.70)	−2.04	0.054

[1] Standard deviation (SD).

The data analysis showed that the two groups were homogeneous, as they were composed of participants who showed similar characteristics in terms of gender ($\chi^2_{(1)} = 2.93$; $p = 0.198$) and the side of the extracted tooth ($\chi^2_{(1)} = 3.67$; $p = 0.194$).

For the assessment of pain level via the NRS, the average score in the TG was 3.91 on day 0, while it was 6.45 in the CG. On day 1, the average score was 3.36 and 5.55 in the TG and CG respectively. On day 3, the average score was 2.59 in TG and 4.18 in the CG. On day 7, the average score was 0.55 in the TG and 2.73 in the CG. A statistically significant difference was observed between groups for the average of the NRS scores on day 0 ($t_{(20)} = -2.48$; $p = 0.022$; $\eta^2 = 0.236$), day 1 ($t_{(20)} = -2.11$; $p = 0.047$; $\eta^2 = 0.183$), and day 7 ($t_{(20)} = -2.45$; $p = 0.028$; $\eta^2 = 0.232$), while no significant difference was found on day 3 ($t_{(20)} = -1.49$; $p = 0.153$; $\eta^2 = 0.099$) (Figure 4).

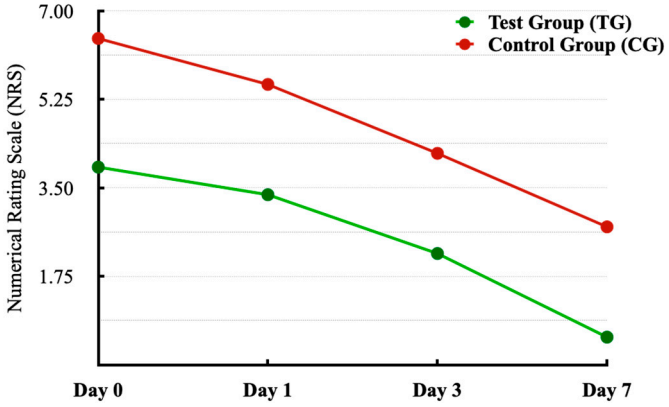

Figure 4. The average pain scores determined via the Numeric Rating Scale (NRS) on day 0, day 1, day 3, and day 7 in the Test Group (TG) and Control Group (CG).

The two-way ANOVA test revealed a significant effect of the group factor, as the CT had greater pain on average than the TG. A significant effect of the time factor was

observed, as the pain decreased significantly in all the measurements carried out. However, the differences between the CT and the TG remained constant over time regarding the NRS score.

The average number of painkillers taken was 4.36 tablets in the TG, while it was 8.18 tablets in the CG. A marginal statistical significance was observed between the two groups in relation to the number of painkillers taken in the considered period ($t_{(20)} = -2.043$; $p = 0.054$; $\eta^2 = 0.173$) (Figure 5). Since these data were obtained from a small sample size, it is reasonable to expect that the observed effect would become statistically significant in the case of a larger sample size.

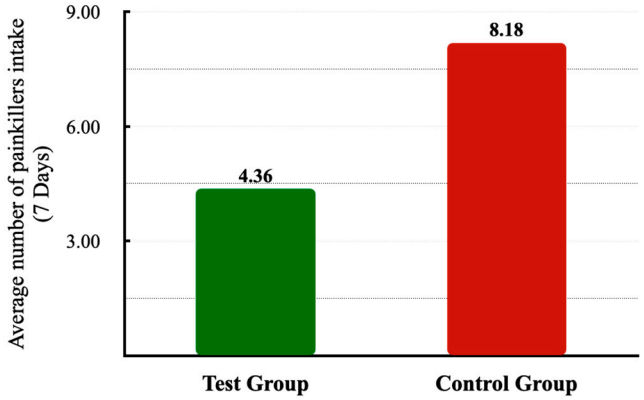

Figure 5. The average number of painkillers taken in the Test Group (TG) and Control Group (CG).

The score of the daily activities questionnaire was calculated for each patient in both groups (Table S1). The TG showed lower scores (lower level of discomfort) than the CG, as the average score of the questionnaire was 8.27 in the TG, while it was 12.73 in the CG. No significant difference was observed between the two groups in relation to the average score of the questionnaire ($t_{(20)} = -1.31$; $p = 0.206$; $\eta^2 = 0.079$) (Figure 6).

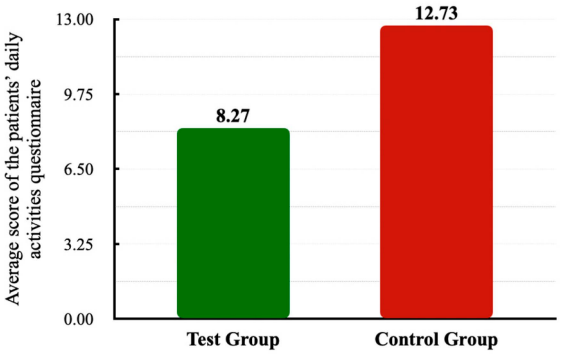

Figure 6. The average score of each patient's daily activities questionnaire in the Test Group (TG) and Control Group (CG).

4. Discussion

In this study, a significant decrease in pain with PBM was observed on day 0, day 1, and day 7 compared to the CG. These positive results may be due to the reported PBM anti-inflammatory, analgesic, and biomodulatory effects. Regarding the absence of statistical differences in pain reduction on day 3 between groups, it has been reported in the literature that the local inflammation around the surgical wound and pain gradually increases and reaches a peak on the second postoperative day, then starts to decrease gradually [29]. This may explain the finding of this study that the difference in pain level was not significant between both groups at day 3, as the level of pain and inflammation normally starts to decrease gradually in both groups.

Although the mechanism of PBM effects is widely studied and many mechanisms have been reported, the exact mechanism has not been completely agreed upon yet [22]. One of the reported mechanisms is PBM's capability to regulate pain perception through inhibiting cyclooxygenase-2, influencing the redox reactions, and downregulating biochemical proteins, such as prostaglandins, interleukins, and tumor necrosis factor [30,31].

Another mechanism is PBM's ability to decrease vessel size and permeability and, consequently, control the influx of proinflammatory cytokines. Some authors have proposed this mechanism as an explanation of an observed less acute inflammatory condition after PBM application [32].

Other studies suggested that PBM can modify pain perception by changing the central uptake and release of serotonin and acetylcholine, stimulating the production of endorphins, and inhibiting bradykinin [20,33].

The positive impact of PBM on the vital capacity, motility, and viability of irradiated cells is also one of the proposed PBM effect mechanisms [34]. The mitochondria of irradiated cells, the first cellular organelles that absorb the laser energy, increase the production of adenosine triphosphate after PBM application, which, consequently, leads to an increase in cellular turnover, including tissue proliferation and oxygenation. These effects, in turn, have a positive impact on tissues that suffer from poor cellular proliferation due to the privilege of an acidic medium after injury [22,35].

PBM's role in the reduction in discomfort after mandibular third molar extraction has been widely studied using a wide range of parameters [22,24,36]. In a recent systematic review, limited evidence of the effect of PBM was observed for the control of pain, edema, and trismus following third molar extractions. This observation might be due to variation in the used wavelengths, parameters, application modality (intraoral, extraoral, or both), protocol timing (preoperative, postoperative, or both), and number of sessions [24]. Defining the effective dose of PBM is a challenging element, as inadequate doses or inappropriate protocols may influence the results.

Regarding wavelengths, it is generally believed that pain and inflammation reduction can be achieved using lasers in the red spectrum. In contrast, the control of edema and trismus can be achieved using lasers in the infrared spectrum due to their greater tissue penetration ability [24,37]. In the literature, the range of the studied wavelengths was from 632.8 nm to 940 nm [22]. The most studied wavelength was 810 nm. In a systematic review, it was found that the majority of the included studies (75.8%) used infrared lasers, and the minority (9.1%) used red lasers [24]. In addition, Duarte de Oliveira et al. observed, in their systematic review, that pain reduction was mostly associated with studies using wavelengths between 660 nm and 830 nm, while studies with wavelengths between 904 and 940 nm showed efficacy on the 2nd postoperative day but not on the 5th, 7th, and 14th postoperative days [23]. Based on the abovementioned findings in the literature, it was suggested that the combination of a red laser, "660 nm", and new wavelength, "445 nm", with near infrared laser, "970 nm", might have a better impact on controlling pain by taking advantage of the different penetration capacities of these wavelengths.

A wide range of PBM parameters were observed in the literature. The power range was from 0.01 W to 1.8 W. The energy per point range was from 3 J/cm^2 to 480 J/cm^2. The irradiation time per point range was from 40 s to 120 s [36]. In the literature, it was reported that studies with power ranges between 10 mW and 200 mW showed effectiveness in pain control [23]. In addition, it was observed in one study that a reduction in pain on the second postoperative day was achieved by using a power of 0.5 W [23,29]. Based on these findings, we decided to use an average power of 200 mW for the intraoral PBM application and 550 mW for extraoral PBM application.

The intraoral application was the most studied application modality, followed by the combined protocols (intraoral and extraoral). The least studied application modality was the extraoral PBM application [24]. In a systematic review, it was noted that studies with combined applications showed better results compared to studies with only extraoral or intraoral applications [36].

Regarding the protocol's timing and the number of sessions, immediate postoperative single-session PBM was the most tested protocol. In a systematic review, it was found that only 1 study out of 17 included studies using both preoperative and postoperative PBM protocols [19,22], and only 2 studies used repeated sessions [38,39]. In a recent randomized clinical trial, the single-session and repeated-session protocols were compared. It was found that there was no difference between the two protocols, and the single-session protocol was recommended [40].

This pilot study aimed mainly to evaluate the effectiveness of this PBM protocol and recognize the improvement points related to this study's design and methodology that could be considered in future randomized clinical trials. Based on this experience, the observed limitations and considerations that should be acknowledged for a better interpretation of the study results and consideration in future studies were as follows: (1) This study was a single-center study, and a multicentric study with a larger sample size is needed to obtain concrete results. (2) This study was a controlled study, and adding a placebo group would give more concrete results due to eliminating the possible risk of bias that may occur. (3) Ensuring equality in the difficulty of surgical extraction between the two groups was only achieved by determining a time limit for the intervention and the standardization of the surgical intervention procedures by the same operator. (4) Only the statuses of other postoperative complications, including trismus and edema, were registered, and all the patients in both groups (TG and CT) experienced trismus and edema. Measuring the level of edema and mouth opening would be helpful in a future study to understand if this PBM protocol has an impact on them. (5) Some concerns should be considered during the interpretation of the obtained results related to the patient's daily activity questionnaire because it is a questionnaire based on previous experience and has not been subjected to a validation process.

5. Conclusions

This pilot study showed a significant reduction in postoperative pain on days 0, 1, and 7 with a single session of intraoral and extraoral PBM. However, the numbers of painkillers taken and the scores of the daily activities questionnaire did not show statistical significance despite the better results observed in patients subjected to PBM. Further studies with the same PBM protocol are needed, taking into consideration the abovementioned limitations.

Supplementary Materials: The following supporting information can be downloaded via this link: https://www.mdpi.com/article/10.3390/app14083268/s1, Figure S1: The patient's daily activity questionnaire translated into Italian; Table S1: The scores of each patient's daily activities questionnaire in both groups.

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Institutional Review Board Statement: All the study procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was approved by the Local Ethical Committee (Prot. n. 775/17, RIF.CE: 4687).

Informed Consent Statement: An informed consent form was signed by all individual participants in this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy protection and ethical restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.

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