ORIGINAL ARTICLES

EFFECTIVENESS OF 650 NM RED LASER PHOTOBIOMODULATION THERAPY TO ACCELERATE WOUND HEALING POST TOOTH EXTRACTION

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Abstract

After tooth extraction, there can be consequences involving injury to the tissue surrounding the extracted tooth, which may lead to severe problems such as inflammation and infection. The wound healing process comprises inflammation, proliferation, and remodeling phases. Photobiomodulation is a therapy form that utilizes the interaction of a light source with tissue. This interaction can activate an increase in Adenosine Triphosphate (ATP), which subsequently triggers a chain reaction leading to the creation of new blood vessels and an increase in the number of fibroblasts. This study used a red laser light source with a power of 3.32 ± 0.01 mW, delivering a dose of 3.5 J to patients for extraction indications. The parameters observed included Interleukin 1β (IL-1β), Prostaglandin E2 (PGE2), Human Beta defensin 2 (HBD2), and Gingival Index (GI). The results of testing saliva samples using the enzyme-linked immunosorbent test (ELISA) for the parameters IL-1β, PGE2, and HBD2 show a significant influence between the control and therapy groups. Meanwhile, GI revealed a significant influence of therapy on the wound-healing process. Using the Mann-Whitney U test, on day 1, the p-value was found to be 0.32, indicating no significant difference between the control and therapy groups. However, on the third day after the therapy was administered, the p-value was obtained as 0.01, signifying a significant difference between the control and therapy groups. On day 5, a p-value of 0.034 was obtained, signifying a significant difference between the control and therapy groups. Based on the research results, it can be observed that there is a decrease in the values of IL-1β, PGE2, HBD2, and GI. This indicates that local immune cells, including resident macrophages, are activated by pro-inflammatory mediators released in response to injury, and they play an essential role in accelerating wound healing.

Key words: wound healing, red laser, photobiomodulation, enzyme-linked immunosorbent (ELISA), gingival index (GI).

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ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ ЛАЗЕРА С ДЛИНОЙ ВОЛНЫ 650 НМ ДЛЯ УСКОРЕНИЯ ЗАЖИВЛЕНИЯ РАН ПОСЛЕ УДАЛЕНИЯ ЗУБА

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Резюме

После удаления зуба могут возникнуть осложнения, связанные с повреждением тканей, окружающих удаленный зуб, что может привести к серьезным проблемам, таким как воспаление и инфекция. Процесс заживления раны включает фазы воспаления, пролиферации и ремоделирования. Фотобиомодуляция — это форма терапии, которая использует взаимодействие источника света с тканью. Это взаимодействие может способствовать выработке АТФ, что впоследствии запускает цепную реакцию, приводящую к образованию новых кровеносных сосудов и увеличению количества фибробластов. В нашем исследовании мы использовали лазер с излучением в красной области спектрв (мощность излучения 3,32 ± 0,01 мВт, световая доза 3,5 Дж). В ходе исследования оценивали влияние терапии на уровень интерлейкина 1β (IL-1β), простагландина E2 (PGE2), бета-дефенсина человека 2 (HBD2) и десневой индекс (GI). Исследования подтвердили значительное влиячние исследуемой терапии на процесс ранозаживления. По результатам исследований также наблюдали снижение значений IL-1β, PGE2, HBD2 и GI. Это указывает на то, что местные иммунные клетки, включая резидентные макрофаги, активируются провоспалительными медиаторами, высвобождаемыми в ответ на травму, и играют важную роль в ускорении заживления ран.

Ключевые слова: заживление ран, красный лазер, фотобиомодуляция, ферментный иммуносорбент (ИФА), десневой индекс.

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Introduction

Currently, 57% of Indonesians experience dental and oral health problems such as caries and periodontal tissue diseases. Periodontal disease is an ailment that affects the tissue surrounding and supporting the teeth, including the gingiva, periodontal ligament, cementum, and alveolar bone [1]. Periodontal disease occurs in developed and developing countries, affecting approximately 20-50% of the global population. The prevalence of periodontal disease in adolescents, adults, and older individuals makes it a public health problem [2]. Periodontal disease is a chronic inflammatory condition of the periodontium, and its advanced form is characterized by the loss of the periodontal ligament and the destruction of the surrounding alveolar bone. It is the leading cause of tooth loss and one of the two most significant threats to oral health [3].

Indications for teeth requiring extraction include severe caries, pulp necrosis, severe periodontal disease, orthodontic reasons, malpositioned teeth, cracked teeth, pre-prosthetic extraction, impacted teeth, supernumerary teeth, teeth associated with pathological lesions, pre-radiation therapy, teeth with jaw fractures, aesthetic considerations, and economic factors. Dental caries that involve the pulp tissue and leave only a tiny amount of healthy tissue make maintenance impossible. Severe periodontal disease causes bone resorption, resulting in tooth mobility, and extraction for orthodontic reasons may be necessary to create space. Malpositioned teeth can cause trauma to the surrounding soft tissues, and teeth with severe fractures may require extraction. Lastly, extractions may be performed for mouth preparation before prosthodontic treatment [4]. Tooth extraction, or simply extraction, is a procedure that involves separating a tooth from the soft tissue that surrounds it and removing a tooth that cannot be retained within its socket using forceps or an elevator. According to survey data, the Indonesian population's total number of teeth affected by decay reached 460 teeth per 100 people (4.6%), and 2.9% of cases of tooth decay required extraction [1]. In dentistry, tooth extraction is a procedure that can lead to injury, causing discomfort for the patient and increasing the risk of infections and other complications, which can result in more severe issues. Additionally, tooth extraction can traumatize blood vessels, initiating a primary hemostasis process that involves the formation of platelet plugs (blood clots) at the site of the wound. Platelet plugs form from interactions between platelets, coagulation factors, and the blood vessel walls [4]. Acute or chronic soft tissue injuries represent an abnormal condition for the patient and necessitate both time and financial resources for treatment. When tissue is damaged due to injury, a wound-healing process is initiated [5].

The wound healing process comprises three phases: the inflammatory phase, the proliferation phase, and the remodeling phase [6]. These phases are interconnected and overlap, beginning from when the wound occurs until healing and wound closure are achieved [7]. When an injury occurs, the body's initial response involves releasing platelets or blood clots, which contain hemostasis components. These platelet aggregates release Transforming Growth Factor beta 1 (TGF β1) as an inflammatory mediator, which activates fibroblasts to synthesize collagen [8]. Tissue healing following a wound is a complex process with several stages, influenced by numerous intrinsic and extrinsic factor [9,10].

The stages of healing are classified into three types: primary, secondary, and tertiary healing [11]. Various therapies are employed for wound healing, one of which is the use of antibiotics. Antibiotics can be pretty effective in treating infections and help prevent pain associated with wound-healing, even though the optimal dosage has not yet been determined. Antibiotics are commonly used to prevent infection during wound-healing, including wounds resulting from tooth extraction surgery. Doxycycline is an antibiotic frequently used for infections caused by gram-negative and grampositive microorganisms [12]. Since the correct dosage has not been established, and its use can potentially be inappropriate for the specific target or even inadvertently affect other areas due to the location of the wound in the mouth, alternative forms of treatment are needed to aid in the wound healing process following tooth extraction.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in periodontal disease therapy as anti-inflammatory drugs. These medications serve to alleviate pain and prevent the spread of inflammation by inhibiting the formation of prostaglandins through the cyclooxygenase (COX) pathway of arachidonic acid metabolism. However, prolonged use of COX-2 inhibitors can lead to adverse effects such as stomach ulcers and hemorrhage [13]. The side effects of non-steroidal anti-inflammatory drugs can encompass gastrointestinal disorders, cardiovascular diseases, and impaired kidney function. In patients with congestive heart failure, the use of non-steroidal anti-inflammatory drugs can exacerbate heart failure and pose risks to the gastrointestinal tract, including bleeding, ulceration, and perforation of the stomach or intestines, which can potentially be fatal. These side effects can manifest anytime during usage without warning symptoms. One issue related to drug usage is Adverse Drug Reactions (ADR) [14]. ADRs refer to adverse reactions to drugs that occur during clinical use. Non-steroidal anti-inflammatory drugs are among the medications most commonly associated with patients requiring treatment for ADRs [15]. Drugs that lead to ADRs are frequently encountered in high-risk patient populations [16]. Therefore, there is a need for alternative therapies that have fewer side effects than using these drugs. Photobiomodulation therapy is one treatment option associated with fewer side effects than drug usage [17,18].

Light sources utilized in photodynamic antimicrobial therapy and photobiomodulation encompass lasers [19] and LEDs [20,21]. Lasers emit coherent, collimated, monochromatic light. The effectiveness of laser therapy is influenced by the wavelength spectrum and energy density [22]. Laser therapy induces biochemical reactions in body tissues to facilitate cell repair, enhance blood circulation, and reduce inflammatory reactions and swelling. The energy delivered by the laser beam stimulates damaged cells to produce adenosine triphosphate (ATP), which is subsequently utilized to maintain normal cellular functions and promote cell repair [23].

Lasers at specific wavelengths have been demonstrated to inhibit the growth of bacteria [24,25] and biofilms [26-28], which are known to cause wound infections in vitro. Low-level laser therapy aims to reduce the toxicity of silver sulfadiazine and promote wound healing. In his literature, Walsh states that low-level laser therapy can impact wound healing [29]. Low-level laser therapy increases fibroblast proliferation, collagen synthesis, angiogenesis, and epithelialization. The laser stimulates the activation of the electron transport chain, ATP synthesis, and a reduction in cellular pH. This, in turn, triggers a reaction in the cell membrane through photophysical effects on calcium channels, resulting in an increased number of macrophages, along with enhanced fibroblast and lymphocyte cell activity [22,30].

Photobiomodulation (PBM), or low-level laser therapy, involves using red light to stimulate healing, alleviate pain, and reduce inflammation [18]. PBM is a therapeutic approach that leverages the interaction of a light source with tissue to trigger an increase in ATP, setting off a chain reaction that leads to the formation of new blood vessels and an increase in the number of fibroblasts responsible for generating a new matrix in injured tissue [31]. The mechanisms of photobiomodulation employ photons (light energy) to modulate biological processes.

PBM laser is also referred to as Low-level laser therapy (LLL), cold laser, therapeutic laser, and soft laser. This device utilizes laser energy, typically generated by a semiconductor diode with power levels ranging from 0.1 W to 0.5 W, for wound therapeutic purposes [2]. The primary chromophores involved are cytochrome c oxidase in mitochondria and calcium ion channels [32]. Secondary effects from photon absorption include increased ATP production, short bursts of reactive oxygen species, elevated nitric oxide levels, and modulation of calcium levels. Tertiary effects encompass the activation of various transcription factors, leading to increased cell survival, enhanced cell proliferation and migration, and the synthesis of new proteins. There is a biphasic dose-response relationship in which low light levels stimulate, while high light levels have an inhibitory effect. It has been discovered that PBM can induce the production of Reactive Oxygen Species (ROS) in normal cells. However, it reduces ROS levels when applied to cells under oxidative stress or in animal disease models. PBM can regulate antioxidant defences and decrease oxidative stress. Research has shown that PBM can activate NF-κB in normal quiescent cells, but in activated inflammatory cells, it reduces inflammatory markers [32]. Therefore, wavelength and dosage are crucial for effectively accelerating wound healing.

One of the benefits of PBM therapy is its ability to enhance the healing process of body tissue wounds. Injured body tissues often undergo a reduction or loss of their anatomical and functional structure. When this occurs, the body's natural mechanisms become crucial in restoring function and structure as part of the natural wound-healing process. To expedite the wound recovery process, a form of stimulation is required to encourage cells to enter the regeneration stage, and photobiomodulation therapy can play a significant role in this regard. As studied by researchers, the use of low-power laser light sources in wound therapy has demonstrated a reduction in pain, a positive impact on inflammation, and facilitation of the proliferation and maturation phases, accompanied by an increase in tensile strength [33].

When lasers are applied to wounds, they induce changes in the permeability of inflammatory cells, leading to increased proliferation, including that of macrophages. As the number of macrophages increases, the expression of TGF-β by these macrophages also increases. Consequently, collagen synthesis is enhanced, resulting in faster and more effective wound healing [34]. Numerous studies have demonstrated the effectiveness of PBM in stimulating wound healing. Research conducted by Gupta et al. (2015) involved wound healing therapy in mice using PBM with a wavelength of 904 nm, which resulted in accelerated healing, reduced inflammation (histologically), decreased expression of TNFα and NF-kB, and increased expression of VEGF, FGFR-1, HSP-60, HSP-90, HIF-1α, and matrix metalloproteinases-2 and 9 compared to the control group [35]. In the research conducted by Astuti et al. (2021), a red laser light source with a wavelength and energy of 3,332 ± 0.01 mW was applied to experimental Wistar rats with wounds resulting from the removal of their first molar teeth. The study aimed to examine the effect of this laser therapy on the wound-healing process. The parameters observed included lymphocyte cells, fibroblast cells, the formation of new blood vessels, Interleukin 1β (IL-1β), and collagen 1α (COL-1α). These observations were compared with two groups of mice that received either 0.1% antiseptic treatment or antibiotic therapy. The results of the observations indicate that red laser photobiomodulation can aid in wound recovery following tooth extraction. This is evidenced by an increase in the number of lymphocyte cells and fibroblast cells, the formation of new blood vessels, the expression of COL-1α, and a decrease in the expression of IL-1β [2].

PBM was discovered almost 50 years ago by Endre Mester in Hungary [37]. PBM is often referred to as low-level laser therapy because the initial devices used were ruby (694 nm) and HeNe (633 nm). Various wavelengths in the red spectrum (600-700 nm) and near-infrared (NIR, 770-1200 nm) range have demonstrated positive results. More recently, blue and green wavelengths have also been explored, but they encounter significant challenges with penetration depth. Therefore, the wavelength highly recommended for reducing pain or wound healing therapy falls within the red spectral range (600-700 nm). It is widely accepted that light penetration into tissue is influenced by its absorption and scattering by molecules and structures within the tissue. Absorption and scattering decrease considerably as wavelength increases, with the maximum NIR penetration depth being approximately 810 nm [18].

Wound healing therapy continues to be a topic of ongoing development in the present day. Correct, effective, and efficient wound management is of utmost importance. The post-extraction wound healing process typically takes a significant amount of time, often up to 16 weeks. The extended duration of the natural wound healing process is primarily due to various disturbances that can occur. These disturbances can be classified into local and systemic factors [38]. Local factors encompass issues such as infection, compromised blood flow, foreign objects that can interfere with the inflammatory mediator response, mobility, and the wound's size, type, and location. On the other hand, systemic factors include considerations like age, nutritional status, the use of glucocorticoids, uncontrolled diabetes, and haematological abnormalities. Considerable efforts have been dedicated to wound care, focusing on the development of novel therapeutic approaches and the application of new technologies for the treatment of both acute and chronic wounds. The wound-healing process following tooth extraction requires a significant amount of time. Therefore, this study aims to investigate the impact of diode laser exposure in post-operative cases of tooth extraction.

Materials and Methods

In this study, there were 60 subjects: 30 in the therapy group and 30 in the control group. The therapy group underwent photobiomodulation therapy using a 650 nm red laser for 60 seconds, with a radiation dose of 2 J/cm^2. This therapy directed perpendicular light onto the injured area immediately after the extraction procedure. Photobiomodulation therapy using a 650 nm red laser was administered on days 1, 3, and 5 following the extraction procedure. Saliva samples were collected from the subjects, with approximately 15 ml of saliva collected from each individual. In contrast, the control group did not receive photobiomodulation therapy.

Laser source

The laser diode light source used in the study is a red laser with a wavelength of 650 nm. Characterization was conducted using a Jasco CT-10 monochromator to determine the peak wavelength. The power output was measured at 3.33 ± 0.01 mW using an OMM-6810B-220 V power meter. The measurement distances ranged from 1 cm to 5 cm, with intervals of 0.5 cm. Diode laser irradiation was performed with exposure times ranging from 300 to 500 seconds, with 1-second intervals. I was characterizing laser exposure temperature involved directing a laser beam at a thermometer sensor and recording the temperature for 1 second for 300 seconds. The irradiation time is determined as follows to calculate the energy density value [25].

$$\text{Energy Density (J.cm}^{-2}) = \text{Intensity (W.cm}^{-2}) \times \times \text{Irradiation Time (s)}. \quad (1)$$

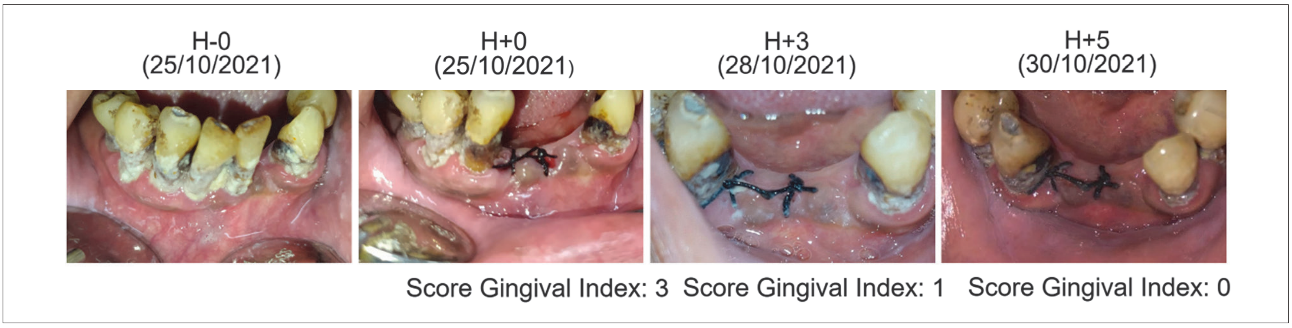

Рис. 1. Оценка десневого индекса.
Fig. 1. Gingival index score.

Gingival Index (GI) Measurement

Samples were collected from gingival index examinations conducted on subjects at the Surgery and Oral Department of RSGM. The baseline data included dental index examinations and the initial saliva collection. The first evaluation occurred after three days of providing laser therapy for gingivitis. The second evaluation was conducted on day five following laser therapy. Gingivitis was assessed using the Gingival Index (GI) developed by Loe and Silness during each evaluation. The Gingival Index scores and corresponding criteria used to determine the gingival status were as follows: 0 (normal gingiva), 1 (mild inflammation characterized by slight changes in colour and mild oedema without bleeding on probing), 2 (moderate inflammation with redness, oedema, and shininess, accompanied by bleeding upon probing), and 3 (severe inflammation marked by pronounced redness and oedema, ulceration with a tendency for spontaneous bleeding) (Anggraini et al., 2016). All scores were recorded, including the gingival index scores of the samples collected before laser therapy (on day 1, day 3, and day 5). The Gingival Index is depicted in Fig. 1.

Enymed-Linked Immunosorbent assay (ELISA)

Enzyme-Linked Immunosorbent Assay (ELISA) was performed using Interleukin 1β (IL-1β), Prostaglandin E2 (PGE2), and Human Beta Defensin 2 (HBD2). ELISA is a biochemical technique employed to detect the presence of antibodies or antigens in a sample. ELISA can test various types of antigens, haptens, or antibodies. The fundamental principle behind the ELISA technique relies on a specific interaction between antibodies and antigens, with enzymes serving as markers. These enzymes produce a signal indicating an antigen's presence if it has reacted with the antibodies. This reaction necessitates using specific antibodies that bind to the antigen (Baker et al., 2007). The ELISA technique is predicated on a specific antigen-antibody reaction with high sensitivity and specificity, utilizing enzymes as indicators. The fundamental principle of ELISA involves analyzing the interaction between antigens and antibodies, with enzymes serving as reaction markers (Yusrini, 2005). ELISA's working principle entails forming a complex between the antigen and antibody, followed by adding specific substrates and peroxidase enzymes. This combination results in a colour change in positive results. ELISA data is typically represented using optical density (OD) values and logarithmic concentrations to generate a sigmoidal curve. This curve can be constructed by direct graphing or by utilizing curve-fitting software in an ELISA reader, such as MS Excel.

Statistical Analysis

In this research, statistical tests were conducted using IBM SPSS to determine if there were significant differences in PGE2, IL-1β, HBD2, and Gingival Index data results. The Independent-Sample T-test was utilized to assess the levels of PGE2, IL-1β, and HBD2, while the Mann-Whitney U test was employed to evaluate the gingival index value.

Results

Interleukin-1β (IL-1β) protein testing was conducted to monitor inflammation during the wound healing process, both before extraction (day 0) and after extraction (day three and day five post-wound occurrence). In general, the observation results indicated a decrease in the levels of IL-1β. The normality test,

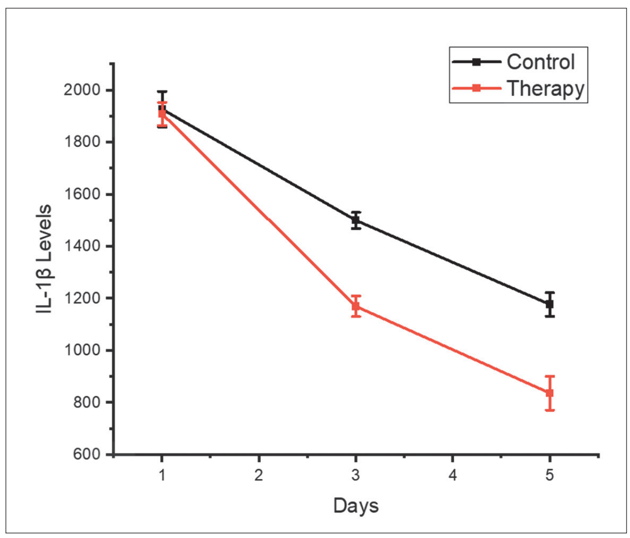

Рис. 2. Динамика уровня интерлейкина-1β в контрольной и терапевтической группах на 1-5 дни.
Fig. 2. Dynamics of Interleukin-1β levels in the control and therapy groups on days 1 to 5.

performed using Kolmogorov-Smirnov, demonstrated that the data exhibited a normal distribution for the control group (without photobiomodulation therapy) with a significance level (α) of 0.300, while for the photobiomodulation therapy group, it was 0.115. Table 1 shows that post-extraction on day 1, day 3, and day five significantly impacted IL-1β levels ($p < 0.05$). All control group subjects exhibited higher IL-1β levels when compared to the photobiomodulation therapy group.

Based on Fig. 2, it is evident that the treatment group receiving 650 nm wavelength red laser photobiomodulation therapy exhibited lower levels of interleukin-1β on day 1, day 3, and day five compared to the control group.

Prostaglandin E2 (PGE2) protein testing was conducted to assess inflammation during the wound healing process on days 1 (pre-extraction) and post-extraction on days three and 5. Overall, the observation results indicate a decrease in the levels of PGE2. The results

Таблица 1
Динамика уровней интерлейкина-β в контрольной и терапевтической группах на 1-й, 3-й и 5-й дни
Table 1
Dynamics of interleukin-1β levels in the control and therapeutic groups on days 1, 3 and 5

Дни Days	Группа Group	N	Среднее Average	Стандартное отклонение SD	Результаты независимого Т-теста Independent T Test Results	
					Результаты Results	Заключение Conclusion
1	Контрольная Control	30	1927.53	68.40	t=7.22	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	1822.20	41.38	p=0.00	
3	Контрольная Control	30	1500.13	30.57	t=41.99	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	1132.10	37.01	p=0.00	
5	Контрольная Control	30	1177.40	45.35	t=25.85	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	820.73	60.44	p=0.00	

Таблица 2
Динамика уровней PGE2 в контрольной и терапевтической группах на 1-й, 3-й и 5-й дни
Table 2
Dynamics of PGE2 levels in the control and therapeutic groups on days 1, 3 and 5

Дни Days	Группа Group	N	Среднее Average	Стандартное отклонение SD	Результаты независимого Т-теста Independent T Test Results	
					Результаты Results	Заключение Conclusion
1	Контрольная Control	30	565.80	10.31	t=5.06	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	554.30	6.96	p=0.00	
2	Контрольная Control	30	493.59	38.55	t=5.48	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	447.23	21.93	p=0.00	
3	Контрольная Control	30	468.07	45.35	t=9.19	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	425.97	20.14	p=0.00	

of the Kolmogorov-Smirnov normality test showed that the data exhibited a normal distribution for the control group (without photobiomodulation therapy) with a significance level (α) of 0.37, while for the therapy group (with photobiomodulation therapy), it was 0.32.

As shown in Table 2, the post-extraction procedures on day 1, day 3, and day 5 had a significant impact on PGE2 levels ($p < 0.05$). The control group subjects had higher PGE2 levels than the photobiomodulation therapy group.

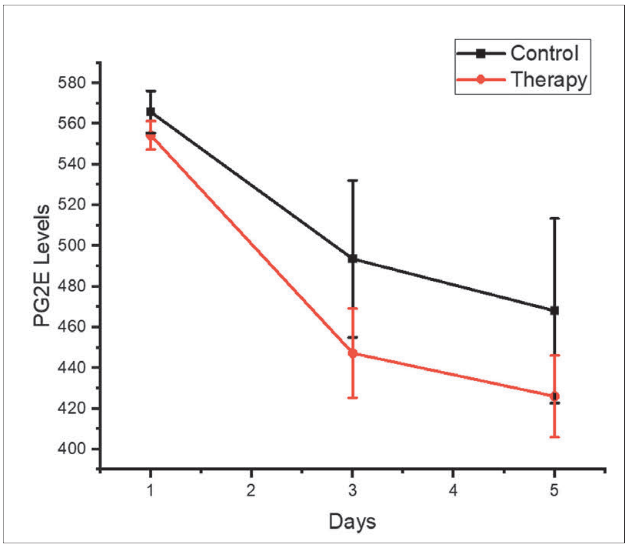

Рис. 3. Уровни PGE2 в контрольной и терапевтической группах в 1-5 дни.
Fig. 3. Dynamics of PGE2 levels in the control and therapy groups on days 1 to 5.

Based on Fig. 3, it is evident that the treatment group receiving 650 nm wavelength red laser photobiomodulation therapy exhibited lower PGE2 levels on day 1, day 3, and day 5 in comparison to the control group.

Human β defensin 2 (HBD2) is a small protein consisting of 15-20 residues that play a role in antimicrobial defence by penetrating microbial cell membranes and inducing microbial death, similar to the action of antibiotics. The observation of the HBD2 protein was conducted to identify indications of inflammation during the wound healing process on day 1 (pre-extraction) and post-extraction on day three and day 5. Overall, the observation results indicate a decrease in the levels of HBD2. The results of the normality test using Kolmogorov-Smirnov revealed that the data exhibited typical distribution characteristics for the control group (without photobiomodulation therapy) with a significance level (α) of 0.186 and for the therapy group (with photobiomodulation therapy), it was 0.171.

Table 3 shows that the post-extraction procedures on day 1, day 3, and day five significantly impacted the levels of HBD2 ($p < 0.05$). The control group subjects exhibited higher HBD2 levels when compared to the photobiomodulation therapy group.

Based on Fig. 4, it is apparent that the treatment group receiving 650 nm wavelength red laser photobiomodulation therapy displayed lower HBD2 levels on day 1, day 3, and day five compared to the control group.

The gingival index (GI) is employed to evaluate gum inflammation severity. It involves measuring six selected teeth, serving as index teeth, including the upper right

Таблица 3
Динамика уровней HBD2 в контрольной и терапевтической группах на 1-й, 3-й и 5-й дни
Table 3
Dynamics of HBD2 levels in the control and therapeutic groups on days 1, 3 and 5

Дни Days	Группа Group	N	Среднее Average	Стандартное отклонение SD	Результаты независимого Т-теста Independent T Test Results	
					Результаты Results	Заключение Conclusion
1	Контрольная Control	30	1864.77	10.31	t=2.29	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	1843.60	6.96	p=0.00	
2	Контрольная Control	30	1817.27	38.55	t=7.22	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	1666.90	21.93	p=0.00	
3	Контрольная Control	30	1659.57	45.35	t=8.28	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	1517.37	20.14	p=0.00	

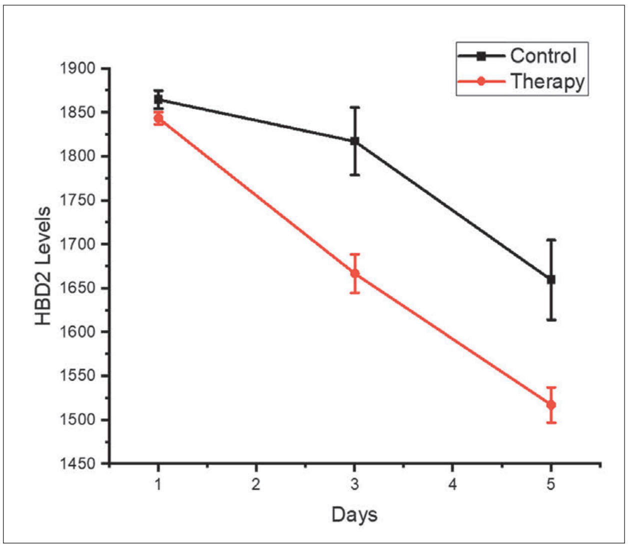

Рис. 4. Динамика уровня HBD2 в контрольной и терапевтической группах с 1 по 5 день.
Fig. 4. Dynamics of HBD2 levels in the control and therapy groups on day 1 to day 5.

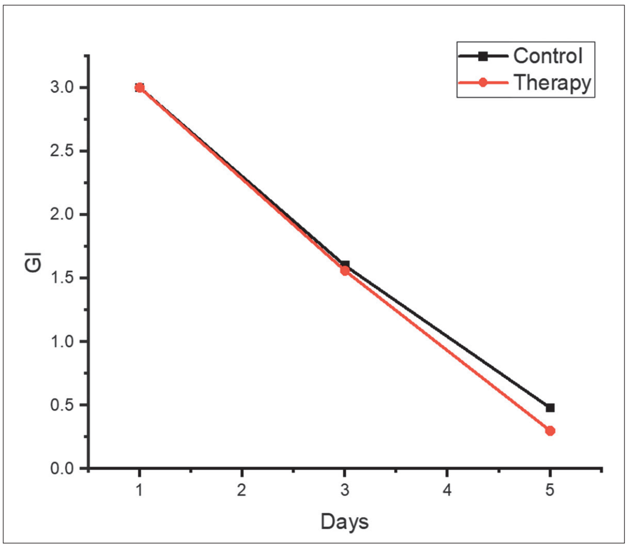

Рис. 5. Динамика десневого индекса в терапевтической группе и контрольной группе с 1 по 5 день.
Fig. 5. Dynamics of GI in the therapy group and control group on day 1 to day 5.

first molar, upper left first incisor, upper left first premolar, lower left first molar, lower right first incisor, and lower right first premolar. GI assesses gum inflammation for each tooth in various aspects (facial, mesial, distal, lingual), assigning a score ranging from 0 to 3 for both the control and therapy groups. A Non-Parametric Test is performed since the data takes the form of interval data.

Based on the outcomes of the non-parametric T-Test for two independent samples utilizing the Mann-Whitney U method, a p-value of 0.32 was obtained on day 1, indicating no significant difference between the control group and the therapy group. However, on day three and day 5, a p-value of less than 0.05 was obtained, signifying a significant difference between the control and therapy groups.

Based on Fig. 4, it is evident that on day 0 and day 1, the GI values were identical, indicating no difference between the control and therapy groups. However, on day three and day 5, differences in GI values were observed. These days, the GI value in the therapy group was lower than the GI value in the control group.

Таблица 4
Динамика десневого индекса в контрольной и терапевтической группах на 1-й, 3-й и 5-й дни
Table 4
Dynamics of Gingival Index levels in the control and therapeutic groups on days 1, 3 and 5

Дни Days	Группа Group	N	Среднее Average	Результаты теста Манна-Уитни Mann-Whitney U Test Results	
				Результаты Results	Заключение Conclusion
1	Контрольная Control	30	3.00	p=0.32	Нет статистически достоверной разницы There is no difference in meaning
	Терапевтическая Therapy	30	3.00		
3	Контрольная Control	30	1.60	p=0.01	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	1.56		
5	Контрольная Control	30	0.48	p=0.03	Статистически достоверная разница There are different meanings
	Терапевтическая Therapy	30	0.30		

Discussion

Tooth extraction is performed in response to issues arising in the oral cavity, such as bacteria, disease, or trauma, that render tooth retention untenable. Following tooth extraction, tissue around the extracted tooth sustains injury. The wound-healing process is the human body's defensive reaction to various injuries. This intricate and dynamic process encompasses inflammation, proliferation, and remodelling phases, each supported by mediators playing specific roles. In response to the wound, the body carries out the physiological function of wound healing. The healing process encompasses three phases: the initial, intermediate, and advanced, each characterized by unique biological processes and cell functions. In the initial phase, hemostasis occurs, during which blood vessels severed in the wound undergo vasoconstriction to halt blood flow. This phase initiates inflammation, clears damaged tissue, and prevents bacterial infection. Chemical agents can assist in the wound-healing process. Low-level laser therapy has long been recognized for stimulating cell activity, including inflammatory cells, which play a pivotal role in wound healing [39].

Photobiomodulation is a device that utilizes coherent, collimated, and monochromatic light energy. It is a light therapy source that significantly relies on the wavelength and energy it employs [35]. Photobiomodulation operates with low wavelengths, energy levels, and doses, enabling it to deliver therapeutic effects to illuminated tissues. Characterization conducted in this research demonstrated that red laser light, with a wavelength of 650 nm, had a measured wavelength and energy of 3.332 ± 0.01 mW. Photon energy is beneficial in augmenting kinetic energy and activating or deactivating enzymes. The response of cells and tissues to growth factors can be observed through various indicators, such as increased ATP and protein synthesis, alterations in cell membrane permeability, calcium ion absorption, cell proliferation, and a series of metabolic changes that ultimately lead to physiological modifications facilitating tissue repair. The favourable clinical outcomes of photobiomodulation (PBM) include anti-inflammatory effects, analgesic properties, pain suppression, and enhanced healing in irradiated tissues. Achieving a specific power density and precise irradiation levels are crucial factors in the interaction between lasers and tissue. Peplow et al. (2010) research emphasized the necessity of using low power levels in photobiomodulation therapy, with dosage playing a pivotal role in its effectiveness [40].

Laser therapy relies on low-intensity lasers or LED lights, mainly through photobiomodulation (PBM) techniques. One of the most intriguing aspects of PBM is its impact on stem cells and progenitor cells, which can lead to increased differentiation rates and ultimately accelerate tissue healing [41]. Numerous studies have indicated that PBM can enhance stem cell proliferation, including gingival fibroblasts and dental pulp stem cells obtained from exfoliated permanent and primary teeth. The effectiveness of PBM on target tissues is contingent on various parameters, including the light source, wavelength, energy density, and duration of laser exposure. Photobiomodulation (PBM) is a non-invasive therapy that effectively reduces inflammation and alleviates pain. It involves the therapeutic use of coherent, collimated, monochromatic, and polarized light absorbed by an endogenous chromophore called cytochrome C. This absorption triggers non-thermal and non-cytotoxic biological reactions through photochemical and photophysical events, ultimately leading to physiological changes.

Low-density energy and specific wavelengths used in PBM therapy facilitate light penetration into cells and tissues, resulting in modulatory effects. These effects include the modulation of inflammation, the proliferation of endothelial cells stimulated by growth factors like VEGF, and increased fibroblast proliferation, which, in turn, enhances collagen synthesis. These events are considered crucial for the proper progression of the healing process. The efficiency of PBM in influencing cellular mechanisms, whether related to proliferation, energy pathways, electrical signal transduction, biochemical processes, or immune activity, is directly dependent on the specific parameters used. These parameters include electromagnetic wavelength, dose, light beam area, tissue specificity, time of exposure, and the type of injury being treated [22].

Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine that plays a role in various physiological processes, including pain, inflammation, and autoimmune conditions. It is primarily produced by activated macrophages. IL-1β has several functions, such as stimulating thymocyte proliferation by inducing the release of interleukin-2 (IL-2), promoting B cell maturation and proliferation, and enhancing fibroblast growth factor activity. Additionally, IL-1β is involved in the inflammatory response, acts as an endogenous pyrogen, and can stimulate the release of prostaglandins and collagenase from synovial cells.

During inflammation, IL-1β levels typically show a significant increase, unlike IL-1α. Type 1 interleukin tends to increase and decrease during the inflammatory process's proliferation phase. In some instances, a significant increase in IL-1β and tumour necrosis factor-alpha (TNF-α) levels may be observed in non-improving foot wounds, indicating ongoing inflammation. The release of IL-1β as a pro-inflammatory cytokine is a natural response during the inflammatory phase of the wound healing process. It is crucial in the body's defence against microorganisms and pathogens. In normal tissue conditions, the expression of IL-1β is generally low. However, during inflammation, the release of IL-1β increases significantly as it contributes to the immune response and the destruction of pathogens in the affected area. This study has shown differences in the levels of IL-1β protein during the wound healing process after tooth extraction when red laser photobiomodulation therapy at a wavelength of 650 nm was applied.

Fig. 2 indicates that the reduction in IL-1β levels was more pronounced in the therapy group compared to the control group. This suggests that photobiomodulation therapy with red laser light reduced this pro-inflammatory cytokine's levels during the healing process. Furthermore, photobiomodulation has also been associated with reduced levels of inflammatory cytokines in nerve injuries, leading to pain reduction and facilitating nerve regeneration, as evidenced by changes in TNF-α, IL-1β, and GAP-43 levels [42].

Prostaglandins play a significant role as inflammatory mediators, and inhibiting prostaglandin production can reduce inflammation. In this study, Prostaglandin E2 (PGE2) levels, which indicate inflammation during the wound healing process, were assessed using enzyme-linked immunosorbent tests (ELISA). The observations revealed a general decrease in the levels of PGE2.

The results of the ELISA tests on saliva samples demonstrated a significant difference between the control and therapy groups. The Independent-Sample T-Test results indicated that on day 1, day 3, and day 5, the red laser photobiomodulation therapy group showed $\alpha<0.05$, signifying a significant difference between the two groups.

This finding is consistent with research conducted by Lim et al. (2015), who investigated the effects of lipopolysaccharide (LPS) from Porphyromonas gingivalis on human gingival fibroblasts (HGF). The study suggests that red laser photobiomodulation therapy has the potential to modulate PGE2 levels, contributing to the reduction of inflammation during the wound healing process [43]. The study by Lim et al. (2015) used Photobiomodulation with a wavelength of 650 nm and applied it to cells exposed to lipopolysaccharide (LPS) either directly or indirectly (by transferring media from PBM-treated cells to other cells with LPS). Both direct and indirect protocols resulted in reductions in various inflammatory markers, including cyclooxygenase-2 (COX2), prostaglandin E2 (PGE2), granulocyte colony-stimulating factor (GCSF), regulated on activated normal T cells expressed and secreted (RANTES), and CXCL11. These findings suggest that Photobiomodulation with a 650 nm wavelength has the potential to effectively reduce inflammation, as indicated by the decreased levels of these inflammatory markers.

The ELISA test results for Human β defensin 2 (HBD2) parameters indicate a difference in the decrease in HBD2 levels between the control and therapy groups. The Independent Sample T-Test results on days 1, 3, and 5 showed a significant difference between the two groups, with $p<0.05$ in each case. This means the therapy group exhibited a more significant reduction in HBD2 levels than the control group. These findings suggest that the red laser photobiomodulation therapy at a wavelength of 650 nm had a notable impact on reducing HBD2 levels, which may contribute to its beneficial effects on wound healing.

In this study, gingival inflammation occurs due to toxins released by bacteria, leading to irritation, redness, and swelling of the gingiva. The degree of gingival inflammation can be assessed using the Gingival Index [46]. The research findings indicated differences in Gingival Index values during wound healing when utilizing red laser photobiomodulation therapy at 650nm. The Mann-Whitney U statistical analysis revealed no significant difference between the control and therapy groups on day 1 ($p=0.32$). However, on the third day, a significant difference was observed with a p-value of 0.01, and on day 5, a significant difference was also noted with a p-value of 0.03. These results suggest that the photobiomodulation therapy group had a lower Gingival Index value than the control group, indicating a positive impact on reducing gingival inflammation.

Conclusion

Based on the research results, it is evident that there is a decrease in the values of IL-1β, PGE2, HBD2, and GI. This indicates that local immune cells, including resident macrophages, are activated by proinflammatory mediators released in response to injury, significantly accelerating the wound-healing process.

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