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Intravascular Laser Blood Irradiation (ILIB) for the Control of Anxiety in Patients Undergoing Lower Third Molar Extraction: A Study Protocol for a Randomized Clinical Trial

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Abstract

Introduction: The extraction of impacted third molars can be an invasive surgery that causes anxiety to the patient. This emotional state can lead to physiological changes that impair the clinical procedure. Therefore, methods for anxiety control have been investigated. A therapy that may present beneficial effects to control dental anxiety during third molar extractions is intravascular blood laser irradiation (ILIB); however, there are no investigations of this therapy on this topic.

Aim: To investigate the effectiveness of ILIB in controlling anxiety in patients undergoing extraction of impacted lower third molars.

Material and Methods: This triple-blinded randomized clinical trial will include 44 patients with an indication to extract one impacted lower third molar. Patients who accept to participate in the study and sign the free and informed consent form, are over 18 years old, without significant systemic disorders, have not previously undergone extraction of third molars, and have a tooth with moderate or minimally difficult level of extraction will be included. Participants will be randomly allocated, from block randomization, into two groups: a placebo group (Group 1; n = 22) that will be submitted to a sham

laser; and an ILIB group (Group 2; n = 22) that will have the radial artery irradiated with a red laser (660 nm), 100 mW, continuous mode, for 30 minutes. The STAI-Y scale will be used to evaluate anxiety before and after the ILIB session. The assessment of blood pressure, oxygen saturation, heart rate, and salivary cortisol level will occur before the application of the STAI-Y and after local anesthesia.

Conclusion: This research may provide new methods to control dental anxiety. The effects of ILIB on salivary cortisol, anxiety status, heart rate, and blood pressure will also be evaluated and may provide evidence about this therapy on controlling these vital signs.

Keywords: Laser Therapy; Low-Intensity Light Therapy; Third Molar; Dental Treatment Anxiety

Introduction

Extraction of third molars is one of the most common procedures in the dentist's routine. Frequently, impacted third molar extractions are surgical and invasive procedures associated with fear and anxiety. Anxiety is an emotional reaction of anguish in anticipation of a future event, often leading to systemic changes, promoting physiological responses that make patient management challenging and can lead to unsuccessful dental care [1,2]. Dental fear and anxiety are highly prevalent and may impact oral health; thus, strategies that prevent these feelings are desirable [3].

Anxiety is associated with vital signs alterations, such as in the heart rate, blood oxygenation, and blood pressure, in addition to changing salivary cortisol (SC) levels [4-6]. In particular, changes in heart rate are described as a reliable measure to determine an individual's anxiety [7]. SC is a hormone secreted by the adrenal cortex through stimuli from the hypothalamus and transmitted to the pituitary gland in stressful situations. Considering that tooth extraction causes disturbance to the individual, this procedure is associated with increased SC levels [8].

Thus, to control anxiety due to third molar extractions, some methods are used, such as pharmacological approaches, herbal medicines [9], auriculotherapy [10], meditation [11], and music therapy [12]. Currently, these approaches have been studied and are shown to be a safe and efficient way to prevent and minimize anxiety in adults undergoing third molar extraction surgery [13]. For example, Midazolam is one of the most common medicines used in the clinical routine for sedation in dental care; however, the herbal medicine *Passiflora incarnata* shows similar efficacy to this drug [9]. Studies on auriculotherapy, meditation, and music therapy show that these therapeutic options may present a potential to be used as non-pharmacological alternatives for anxiety control and sedation during third-molar extraction [10-12]. However, these therapies often need specialized professionals, which may enhance the surgery costs. Therefore, studies on novel approaches that control anxiety are encouraged.

A promising therapy that has been studied and presents beneficial results in controlling vital signs is the Intravascular Laser Blood Irradiation (ILIB), on its modified technique [7,14]. It consists of continuously irradiating the site of the radial artery with a low-power red laser. This treatment brings benefits regarding pain control, improvement in blood circulation, and modulation of inflammation by inhibiting the production of prostaglandins [15,16]. Furthermore, studies suggest that it may have an anxiolytic effect on pediatric patients, modulating hormones that act on anxiety [7]. However, to date, there are no studies that have evaluated the effectiveness of ILIB on the control of anxiety in patients undergoing third molar extraction.

Thus, considering that studies on this subject are scarce, it is of great interest that clinical trials provide better information in the area that may contribute to the dental care practice. Herein, we present a study protocol that will evaluate the effectiveness of using ILIB in controlling anxiety in patients undergoing surgical extraction of impacted lower third molars. This study hypothesizes that ILIB will reduce anxiety, maintain vital signs, and control SC levels.

Material and Methods

This is a triple-blind randomized clinical trial that will be carried out with patients who will undergo third molar extraction and will be submitted to ILIB or a placebo group. The study was approved by the institution's ethics committee (CAAE number: 70342023.0.0000.5076) and registered in the Brazilian Clinical Trial Registry (REBeC: RBR-9ycg67p). This study followed recommendations from the SPIRIT guide for clinical trials [17]. Figure 1 demonstrates the study flow and Figure 2 demonstrates the study flowchart.

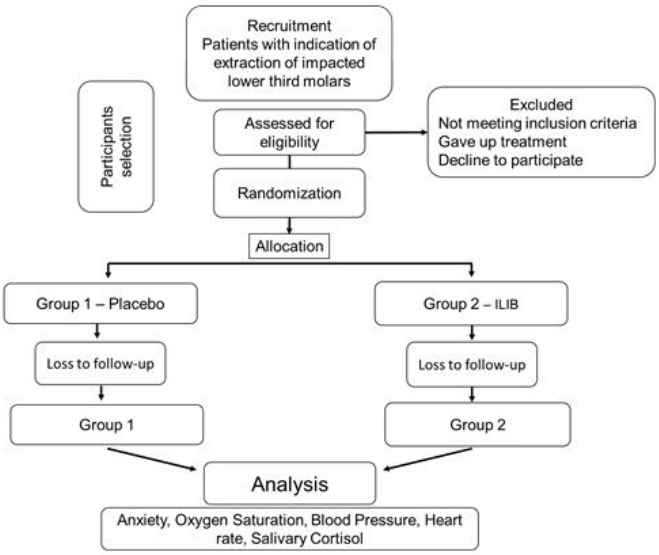

Figure 1: Study flow according to SPIRIT guideline

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation*			
TIMEPOINT	$-t_1$	t_0	t_0	t_1	t_2	t_3
ENROLMENT:						
Eligibility screen	X					
Third molar evaluation	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
[ILIB]				X		
[CONTROL]				X		
ASSESSMENTS:						
[Cortisol]			X		X	X
[STAI-Y]			X		X	
[Blood pressure]			X		X	
[O_2 Saturation]			X		X	
[Heart rate]			X		X	
[Clinic demographic data]			X			

Figure 2: Flowchart of the study

Participants

Patients who will undergo surgery to extract an included third molar will be selected from the UniEvangélica Dental Teaching Clinic, in the Oral Surgery discipline. The Openepi software, available on the website http://www.openepi.com, was used to calculate the sample size, considering the prevalence of patients with moderate or high anxiety according to a study by Gurram et al [11]. For this calculation, parameters were considered as a significance level of 95% (1 – α type I error), study power of 80% (1 – beta type II error), and sample size ratio between exposed and unexposed of 1.

To date, there are no studies that evaluated the effect of ILIB on dental anxiety; therefore, the study by Gurram et al [11] was considered for the sample calculation. In the cited study it was evaluated the effect of meditation, a non-pharmacological method, on the anxiety levels of patients undergoing surgical extraction of impacted third molars. It was considered that the percentage of non-exposed (placebo group) and exposed (intervention group) positive individuals were 64% and 19%, respectively. Therefore, the number of individuals to be included in the present study will be 44 participants, considering continuity correction.

The study inclusion criteria will be: patients who accept to participate in the study and sign the informed consent form, over 18 years old, ASA I or II classification [18], who have not previously undergone tooth extraction of third molars, with indication of extraction of at least one lower third molar, with a moderate or minimally difficult level of difficulty according to Pederson's classification [19]. This classification will be performed by a previously trained researcher, using the panoramic X-rays of the patients eligible for the study.

The exclusion criteria will be patients with signs of infection or inflammation near the teeth indicated for extraction, with psychiatric disorders, cognitive distortions that impair the questionnaire interpretation and application, patients using anxiolytic or antidepressant medications, pregnant women, and patients who do not have at least one radial artery available for ILIB therapy.

Patients will be invited at the time of their surgery consultation, immediately before the surgical extraction. Recruitment will occur until the number of patients is reached. The surgery will be performed by students in the last year of the Dentistry course, under the guidance of professors specializing in oral and maxillofacial surgery. The study will be discontinued in case of severe collateral effects. This study does not plan an analysis of partial results.

Randomization and Blinding

Participants will be randomly assigned into two groups: Group 1 (Placebo) and Group 2 (ILIB). Randomization will be carried out to ensure the formation of groups with a fixed number of individuals. The electronic generator "www.sealedenvelope.com" will be used for block randomization, with four participants per block. A collaborator who will not actively participate in the clinical trial will be responsible for generating the random sequence and sealing it in opaque envelopes. The numbers 1 and 2 will be used to identify the participant's allocation group. The patient will be allocated to the group before the surgical procedure, after collecting vital signs data and applying the questionnaires, immediately before the ILIB or placebo session.

The patient will be blinded to the allocated group. For this, one of the researchers will instruct the participant to close their eyes and wear a blindfold, until the researcher places a black tape on the laser beam that will prevent it from irradiating the radial artery. Furthermore, an opaque black fabric that prevents the passage of light will be used, ensuring the patient's blinding. The researcher responsible for measuring vital signs and applying the questionnaire, and the one responsible for statistical analysis of the data, will also be blind to the participants' group.

Study Groups

Group 1 (Placebo)

Patients in this group (n=22) will undergo placebo treatment with a sham Laser. Low-power laser equipment (InGaAlP) will be used coupled to a bracelet (LaserDuo, MMOptics Equipamentos, Sao Carlos, Brazil), worn on one of the wrists of the participant, over the radial artery. The equipment will be programmed in ILIB-1 mode, however, the laser beam exit will be covered with black tape that will prevent the passage of light, thus, no energy will be irradiat-

ed to the patient. An opaque black fabric will be placed over the laser equipment and the patient's arm to ensure participant blindness. After the programmed time of 30 minutes, the equipment will emit a characteristic sound that identifies the end of the therapy. Before each participant, the laser tip will be disinfected with a 70% alcohol solution. The equipment will be kept on the charger while not in use.

Group 2 (ILIB)

Participants in this group (n=22) will undergo the ILIB session using the equipment mentioned above (LaserDuo, MMOptics). The protocol will be based on a previous study [7]. For therapy, the ILIB.1 mode of the equipment will be selected, which has as parameters: wavelength of 660 nanometers (red laser), 100 mW of power, continuous mode, with light irradiation for 30 minutes, laser beam exit area of the $3mm^2$.

The equipment will be positioned over the radial artery and fixed with the manufacturer's bracelet. The irradiation will be punctual and as perpendicular as possible. In the same way as for the previous group, an opaque black fabric will be placed over the laser equipment and the patient's arm. Before each participant, the laser tip will be disinfected and wrapped in a plastic film. The equipment will be kept on the charger while it is not being used and at the beginning of each working day, the power of the equipment used will be measured using Laser Check (MMOptics Equipments).

Outcomes

Anxiety

Dental treatment anxiety will be the main outcome and will be assessed using the Portuguese-translated version of the State-Trait Anxiety Inventory, Form Y (STAI-Y) questionnaire [20,21]. The questionnaire will measure anxiety status before and after the ILIB/placebo session. The STAI-Y questionnaire in T-1 form will be used in this research to consider the current status of anxiety.

The questionnaire has 20 questions with four alternatives each, in which the patient must indicate whether they strongly agree or do not agree at all with the statement. The score of the items will be summed to obtain the respective total score, which may vary between a minimum of -30 (low anxiety) and a maximum of 50 points (high anxiety). The items related to the absence of anxiety are scored inverted (i.e., the items: 1, 2, 5, 7, 9, 11, 12, 15, 19, 20).

The participant will answer the questionnaire after the acceptance of the signed informed consent and before the ILIB/placebo session. The time to complete the questionnaire is approximately 10 minutes. If there is difficulty in understanding any question, the patient may request an explanation from the researcher responsible for applying the instrument. The STAI-Y will be applied again, through an interview, after four minutes of the anesthesia of the tooth to be extracted. According to Gadve et al. [22], this time corresponds to the maximum heartbeat recorded during surgery to extract third molars.

Vital Signs

The participants' vital signs will be assessed at two moments: before the STAI-Y questionnaire interview and four minutes after the local anesthesia.

Diastolic and systolic blood pressures will be measured using an electronic pressure monitor with an attached cuff (HEM-7122, Omron, Kyoto, Japan). To guarantee calibration, charged batteries will be used. The evaluation of heart rate and oxygen saturation will be conducted by using a pulse oximeter (OLED GRAPH, GTech Brasil Ltda, São Paulo, Brazil), after an observational period of approximately 15 seconds, the research will register the higher value noted for heart rate and oxygen saturation.

Molecular Study

Saliva sample collection

Saliva collection to assess the level of SC will be carried out in two moments: after the STAI-Y first assessment, in the questionnaire application room, in a calm environment, with artificial lighting, which allows the participant to sit down; and in the second moment, saliva will be collected after local anesthesia, with the participant sit on the dental chair.

The participants will be instructed to rinse their mouths with water to eliminate possible food residues. A

specific kit will be used to collect saliva (Sarstedt Inc., Nümbrecht, Germany), and a cotton roll will be positioned in the participant's mouth, on the floor of their mouth, who will be instructed to remain quiet, with their head slightly tilted forward. After approximately two minutes, or after noticing that the cotton is soaked in saliva, the cotton roll will be removed. After collection, the Salivette tubes (Sarstedt Inc.) will be kept in a thermal box with ice until centrifugation. The samples will be centrifuged at 4,500 rotations/minute (rpm) for 15 minutes and stored in 2mL Eppendorf tubes, after which they will be stored in a -4°C freezer until the SC tests are carried out.

SC Assessment

For this assay, the competitive ELISA test will be used using the Enzyme Immunoassay kit (Salimetrics Kit, LLC, USA), according to the manufacturer's instructions. Briefly, the samples will be mixed, centrifuged, and deposited in each well of a 96-well plate coated with the antibody. After this, the enzyme conjugate will be added and the plate will be agitated using a microplate shaker. The wells will be washed with a buffer solution and the substrate will be added. Finally, a new wash and pipetting of the reaction-stopping solution will be carried out.

The assay will be read in a spectrophotometer with an absorbance of 450nm. To determine the concentration of each sample, a standard curve will be constructed, according to the manufacturer's determinations, and the absorbance values obtained will be transformed into the cortisol concentration in μg/dL.

Clinical and Epidemiological Data

Information will be collected from participants' records such as name, city of origin, age, sex, level of education, and difficulty in extracting the third molar. This data will be collected using a specific form created by the researchers. After the ILIB / placebo session, participants will be asked to answer whether they would recommend the therapy to other patients, whether they felt any discomfort, or if they would like to share their experiences.

Statistical Data Analysis

Comparison of the clinical and demographic characteristics of patients between the two groups will be performed using the Pearson Chi-square test for categorical variables. To compare the anxiety status, blood pressure, and heart rate, the Kolmogorov-Smirnov normality distribution test will be performed to determine the most appropriate test for each comparison (Wilcoxon and Mann-Whiney, or ANOVA and t-test of Student). The Wilcoxon test will be used to compare SC values at different times within the group. The Mann-Whitney test will be used to compare SC between groups. The p-value <0.05 will be considered statistically significant. Statistical analysis will be performed using the IBM SPSS 24.0 statistical package (SPSS Inc., Chicago, IL, USA).

Discussion

This is a research protocol to investigate the role of systemic laser irradiation in controlling dental anxiety. The use of LASER in dentistry is well established, mainly in relation to its use as photobiomodulation therapy, high-power lasers, and photodynamic therapy [15,16,23]; however, the literature lacks information about systemic LASER therapy, especially in Dentistry [15].

The extraction of included third molars often requires minor oral surgery techniques, and because of that, it is usually associated with dental anxiety that can cause systemic effects that hinder the surgical procedure [24]. Besides that, patients with high anxiety traits may experience a worse postoperative recovery [25]. In this way, methods to control dental anxiety have been proposed. The pharmacological method is the most used and studied [9]; however, the possible side effects must be considered and may limit their use [26]. In this way, non-pharmacological approaches have been proposed [13].

Auriculotherapy, meditation, and music therapy are non-pharmacological methods that demonstrate an effect on controlling dental anxiety during surgical extraction of third molars [10-13]. However, these alternative therapies require qualified professionals so that they can be routinely used. Therefore, other methods must be investigated, we highlight that ILIB may have anxiolytic effects [7]. There is still a lack of evidence to justify the use of ILIB on anxiety control; however, it is highlighted that it is a promis-

ing therapy, easy to perform, and of low cost, which can help control dental anxiety.

ILIB may improve vital signs, especially oxygen saturation, hematological parameters, blood pressure, and heart rate [7,27]. It is important to highlight that anxiety promotes changes in heart rate, and the maximum peak of heartbeat in the surgical extraction of third molars occurs approximately 4 minutes after local anesthesia [22], because of this, this was one of the periods chosen for assessment. We believe that due to the effect of ILIB on heart rate, this therapy may also demonstrate an effect on controlling anxiety in patients undergoing third molar extraction.

Additionally, ILIB gained notoriety during the COVID-19 pandemic, when an effect of its use on the oxygen saturation levels of individuals infected with the SARS--CoV2 virus was demonstrated [14]. It is suggested that ILIB may be effective in treating the main causes of death resulting from COVID-19, which are pulmonary edema, pneumonia, and acute respiratory distress syndrome [14]. Although we will not include patients with oxygen saturation impairment, we believe that in this study, ILIB will help in the maintenance of the normal parameter of this vital sign.

Despite the variety of protocols described for ILIB [7,14,27-29], the protocol adopted in the present research it will be based on the manufacturer's guidance and previous study, that also used red light and an irradiation time of approximately 30 minutes [7]. According to Zhao et al [30], the therapy uses the intensity at the tip of the optic fiber about 10^3 mW/cm^2, and considering the speed of blood cells, the time of each blood cell is about 10 ms, each blood cell receives an energy about 100 J/m^2. In the present study, the parameters that will be used are similar to those described, the power density at the tip is approximately 3,333 mW/cm^2, and each blood cell will receive 333 J/cm^2. The time of irradiation in the literature is described as 30min up to 60min [31-33], to try to irradiate all blood cells in a reliable time, that would be reproducible in ambulatory settings, in the present study the irradiation time will be 30 minutes [7, 33].

Additionally, the target of the ILIB is Oxyhemoglobin, this molecule presents a higher absorption coefficient when red light is used, whereas above 600nm melanin and water show peaks of light absorption [34,35]. Additionally, longer wavelengths present a higher depth penetration, thus it would be rational to use the red laser, to guarantee that the photons would be absorbed by the oxyhemoglobin and improve the oxygen carrying of the blood, not by the melanin [34,36,37].

The therapy adopted can also result in accelerated healing and reduce the surgical side effects, since ILIB may present a potential for increased tissue repair and control of the inflammatory process [27]. However, in this study, the effects of ILIB on tissue repair and its anti-inflammatory effect will not be evaluated, as this would be associated with a higher cost, longer patient follow-up time, and the need to control the researcher responsible for the extraction.

SC is a hormone released in stressful situations that aims to control this emotional state; thus, it is also released in anxiety situations [38]. To date, few studies have investigated the action of ILIB on SC levels in dental procedures [7]. The results of the present study may be important not only to investigate the possible effect of the ILIB on anxiety control during dental treatments but also in other conditions related to dysregulated cortisol levels, such as cardiovascular diseases, stroke, and as a possible mediator of an association between Alzheimer's and diabetes mellitus [39-41].

Regarding the STAI-Y, it is important to point out that several instruments measure anxiety or dental fear; however, most of these instruments are related to the trait of general anxiety, not anxiety status at the time of assessment [42,43]. Thus, to measure the current status of anxiety, at the time of the third molar extraction or immediately before it, the first part of the STAI-Y questionnaire will be used [20,21], we believe that it will reflect in a more appropriate assessment of patient's anxiety before and during third molar extraction.

Finally, we believe that ILIB will be effective in controlling anxiety in patients who will undergo the extraction of impacted third molars, as the systemic LASER presents promising results in controlling the vital signs related to dental anxiety. The nature of this research, a randomized controlled clinical trial with a placebo group, will be important to determine whether the effect comes from the thera-

py adopted, or because the patient remains without activities for around 30 minutes in a calm environment. Therefore, the originality of this research may promote evidence of ILIB in controlling dental anxiety, SC levels, heart rate, and oxygen saturation.

Conclusion

The results of the research protocol presented may provide evidence on the ILIB effects on dental anxiety, SC, and vital signs related.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Silveira ER et al. (2021) Estimated prevalence of dental fear in adults: A systematic review and meta-analysis. J Dent 108: 103632.

2. Appukuttan DP (2016) Strategies to manage patients with dental anxiety and dental phobia: literature review. Clin Cosmet Investig Dent 8: 35-50.

3. Robison OJ et al. (2013) The impact of anxiety upon cognition: perspectives from human threat of shock studies. Front Hum Neurosci 7: 203.

4. Cunha SR et al. (2021) Herbal medicines as anxiolytics prior to third molar surgical extraction. A randomized controlled clinical trial. Clin Oral Investig 25: 1579-86.

5. Hosgor H, Coskunses MF, Tokuc B (2021) Correlation between preoperative pressure pain assessments and anxiety and postoperative pain in impacted lower third molar surgery. J Korean Assoc Oral Maxillofac Surg 47: 15-19.

6. Yildirim O, Turkmenoglu K, Mollaoglu N (2022) Assessment of Relationship between Hemodynamic Changes and Anxiety in Patients During Lower Third Molar Surgery. J Coll Physicians Surg Pak 32: 1524-8.

7. Rangel GRC, Pinheiro LS (2021) Laser acupuncture and intravascular laser irradiation of blood for management of pediatric dental anxiety. J Oral Sci 63: 355-7.

8. Gadicherla S et al. (2018) Estimation of salivary cortisol among subjects undergoing dental extraction. J Clin Exp Dent 10: e116-9.

9. Dantas LP et al. (2017) Effects of passiflora incarnata and midazolam for control of anxiety in patients undergoing dental extraction. Med Oral Patol Oral Cir Bucal 22: 95-101.

10. Dellovo GE (2019) Effects of auriculotheraphy and midazolam for anxiety control in patients submitted to third molar extraction. Int J Oral Maxillofac Surg 46: 669-74.

11. Gurram P et al. (2021) Effect of Heartfulness Meditation on Anxiety and Perceived Pain in Patients Undergoing Impacted Third Molar Surgery. J Oral Maxillofac Surg 79: 1-7.

12. Monteiro CGJL et al. (2022) Does listening to music reduce anxiety and pain in third molar surgery? -a systematic review. Clin Oral Invest 26: 6079-86.

13. Wong MSN et al. (2022) Non-Pharmacological Interventions for Reducing Fear and Anxiety in Patients Undergoing Third Molar Extraction under Local Anesthesia: Systematic Review and Meta-Analysis. Int J Environ Res Public Health 19: 11162.

14. Matos BTL et al. (2021) Photobiomodulation Therapy as a Possible New Approach in COVID-19: A Systematic Review. Life (Basel) 11: 580.

15. Tomé FFR et al. (2020) ILIB (intravascular laser irradiation of blood) as an adjuvant therapy in the treatment of patients with chronic systemic diseases—an integrative literature review. Lasers Med Sci 35: 1899-907.

16. Fu CMJ et al. (2022) The Adjuvant Therapy of Intravenous Laser Irradiation of Blood (ILIB) on Pain and Sleep Disturbance of Musculoskeletal Disorders. J Pers Med 12: 1333.

17. Chan A et al. (2013) SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 346: e7586.

18. American society of anesthesiologists (2023) ASA Physical Status Classification System, Treasure Island (FL): StatPearls Publishing.

19. Pederson GW (1988) Surgical removal of tooth. In: Pederson GW. Oral surgery. Philadelphia: WB Saunders.

20. Daniel F (1995) Avaliação psicometrica da ansiedade – Aplicação do STAI-Y de Spielberger a uma amostra da população Portuguesa. Comunicação apresentada no VII Congresso Ibero-Americano e no IV Congresso de Psiquiatria da Língua Portuguesa. Universidade Fernando Pessoa. Porto.

21. Silva D, Correia S (1997) STAI – "O Inventário de Estado-Traço de Ansiedade".

22. Gadve VR et al. (2018) Evaluation of Anxiety, Pain, and Hemodynamic Changes during Surgical Removal of Lower Third Molar under Local Anesthesia. Ann Maxillofac Surg 8: 247-53.

23. Kalhori KAM et al. (2019) Photobiomodulation in Oral Medicine. Photobiomodul Photomed Laser Surg 37: 837-61.

24. Suleiman AR et al. (2021) The effect of dental anxiety on surgical time of mandibular third molar disimpaction. Niger J Clin Pract 24: 1430-7.

25. Lago-Mendéz LL, Diniz-Freitas M, Senra-Rivera C (2009) Postoperative recovery after removal of a lower third molar: role of trait and dental anxiety. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 108: 855-60.

26. Li X, Liu Y, Li C, Wang J (2023) Sedative and adverse effect comparison between oral midazolam and nitrous oxide inhalation in tooth extraction: a meta-analysis. BMC Oral Health 23: 307.

27. Malavazzi TCS et al. (2023) Effects of the invasive and non-invasive systemic photobiomodulation using low-level laser in experimental models: A systematic review. Lasers Med Sci 38: 137.

28. Sertaje MRF et al. (2022) Vascular photobiomodulation in the treatment of children with temporomandibular disorders: Study protocol for a randomized, controlled, blind, clinical trial. Medicine (Baltimore) 101: e31228.

29. Viarengo NO et al. (2022) Evaluation of intravascular irradiation of blood in children with sleep bruxism: Study protocol for a randomized controlled clinical trial. Medicine (Baltimore) 101: e31230.

30. Zhao SD et al. (2008) Meta-analysis on Intravascular Low Energy Laser Therapy. Proceedings of SPIE 7280: 728012-2-728012-13.

31. Fu JCM et al. (2022) The Adjuvant Therapy of Intravenous Laser Irradiation of Blood (ILIB) on Pain and Sleep Disturbance of Musculoskeletal Disorders. J Pers Med 12: 1333.

32. Lin YP et al. (2023) Effects of intravascular photobiomodulation on cognitive impairment and crossed cerebellar diaschisis in patients with traumatic brain injury: a longitudinal study. Lasers Med Sci 38: 108.

33. Lizarelli RFZ et al. (2021) A pilot study on the effects of transcutaneous and transmucosal laser irradiation on blood pressure, glucose and cholesterol in women. Heliyon 7: e07110.

34. Enwemeka CS (2009) Intricacies of Dose in Laser Phototherapy for Tissue Repair and Pain Relief. Photomedicine and Laser Surgery 27: 383-93.

35. Patterson MS, Wilson BC, Wyman DR (1991) The Propagation of Optical Radiation in Tissue II: Optical Properties of Tissues and Resulting Fluence Distributions. Lasers Med Sci 6: 379-90.

36. Mikhaylov VA (2015) The use of Intravenous Laser Blood Irradiation (ILBI) at 630–640 nm to prevent vascular diseases and to increase life expectancy. Laser Ther 24: 15-26.

37. Xu Y, Lin Y, Gao S (2015) Study on the selection of laser wavelengths in the intravascular low-level laser irradiation therapy. Lasers Med Sci 30: 1373-6.

38. Pulopulos MM, Baeken C, de Raedt R (2020) Cortisol response to stress: The role of expectancy and anticipatory stress regulation. Hormones and Behavior 117: 104587.

39. Iob E, Steptoe A (2019) Cardiovascular Disease and Hair Cortisol: a Novel Biomarker of Chronic Stress. Curr Cardiol Rep 21: 116.

40. Barugh AJ et al (2014) Cortisol levels and the severity and outcomes of acute stroke: a systematic review. J Neurol

261: 533-45.

41. Notarianni E (2017) Cortisol: Mediator of association between Alzheimer's disease and diabetes mellitus? Psychoneuroendocrinology 81: 129-37.

42. Bonafé FSS et al. (2016) Validation and Invariance of the Dental Anxiety Scale in a Brazilian sample. Braz Oral Res 30(1): e138.

43. Dereci O et al. (2021) The Comparison of Dental Anxiety between Patients Treated with Impacted Third Molar Surgery and Conventional Dental Extraction. Biomed Res Int 2021: 7492852.