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INSTITUTO DE PESQUISAS ENERGÉTICAS E NUCLEARES
Mestrado Profissional em Tecnologia das Radiações em Ciências da Saúde

Non-ablative treatment of sleep breathing disorders with the association of two high-intensity pulsed lasers: Nd:YAG and Er:YAG.

VALERIA MENDES

Dissertação apresentada como parte dos requisitos para obtenção do Grau de Mestre Profissional em Tecnologia das Radiações em Ciências da Saúde na Área de Concentração
Processos de Radiação na Saúde

Orientadora:
Profa. Dra. Denise Maria Zezell

São Paulo
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Banca Examinadora

Profa. Dra.: Denise Maria Zezell

Instituição: IPEN   Julgamento: Aprovada

Profa. Dra.: Thays Crosara A. Cunha

Instituição: ABROS   Julgamento: Aprovada

Prof. Dr.: Walter Silva Junior

Instituição: Instituto Walter Silva   Julgamento: Aprovada

Dedico a realização deste trabalho aos mais de 1.000.000.000 de indivíduos em todo mundo que apresentam problemas respiratórios obstrutivos durante o sono. E dentre estes, a um em especial, meu pai, que me impulsiona todos os dias a buscar caminhos e opções de tratamento. Sua história de dedicação ao trabalho e à família ao longo de toda vida, me inspira. Hoje eu retribuo. Espero que nos lembremos desse dia com alegria.

Com amor,
Valeria.

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A Deus, pela vida.

Ao universo, por sempre conspirar a meu favor.

Aos meus pais, pela vida, pelo seu exemplo, amor e cuidado. Sempre e para sempre.

À minha irmã, pela sua presença sempre amorosa. Sempre e para sempre.

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À minha filha, Ana Luiza, por me permitir viver o maior amor que existe no mundo. Pelo incentivo, pela ajuda. Por me apresentar a solução para um problema de pesquisa. Pelas edições dos vídeos para as apresentações. Pelos incontáveis sorrisos a cada novo dia. Sempre e para sempre.

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Aos colegas do CLA, pela presença, apoio e incentivo.

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À minha amiga Stefania, pela ajuda e confiança.

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<div align="right">

Muito obrigada!
Valeria.

</div>

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À querida e sempre presente, a qualquer hora do dia, da noite, aos finais de semana e nos momentos mais importantes, Profa. Dra. Denise Maria Zezell, minha orientadora, por seu exemplo de competência, integridade, conduta e visão profissional, mas antes de tudo, pelo ser humano que é.

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Obrigada pelo seu tempo, por acreditar em mim (até quando eu não acreditei que daria conta!) e por investir no meu desenvolvimento intelectual e profissional. Por possibilitar que eu fizesse o meu melhor. Não foi fácil, mas valeu cada minuto de dedicação a este trabalho. Você fez a diferença.
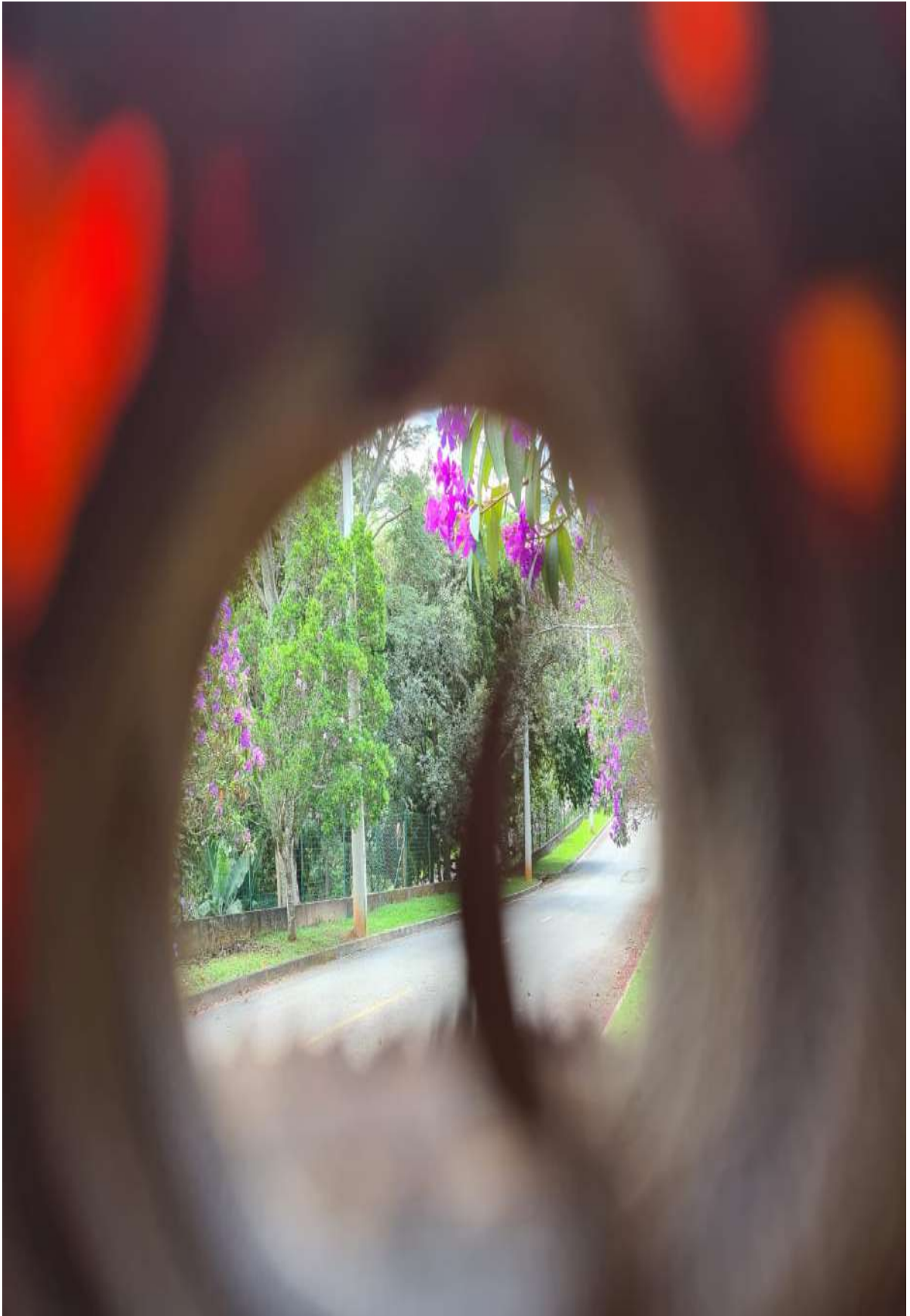
Foi uma honra para mim, receber sua orientação.

Conte comigo para o que for preciso.

Sigo no foco.

Gratidão! Sempre e para sempre.

Com toda admiração desse mundo,

Valeria.

RESUMO

Mendes V. Tratamento não-ablativo dos distúrbios respiratórios do sono com associação de dois lasers pulsados de alta intensidade: Nd:YAG e Er:YAG. São Paulo. Dissertação (Mestrado Profissional em Tecnologia das radiações nas Ciências da Saúde) – Instituto de Pesquisas Energéticas e Nucleares, IPEN-CNEN/SP; 2022.

Ronco primário e apneia obstrutiva do sono são considerados distúrbios respiratórios do sono (DRS) e representam os diferentes graus de severidade de uma mesma doença crônica, complexa e progressiva, que afeta em torno de um bilhão de pessoas em todo o mundo. É mais prevalente em homens idosos. Historicamente, o ronco é visto como problema social, sendo considerado a forma mais benigna de DRS. Por conta disso, o tratamento não é prescrito. O ruído é causado pela vibração dos tecidos moles na região de maior constrição das vias aéreas superiores (VAS). As opções terapêuticas podem envolver tratamentos médicos, uso de dispositivos e procedimentos cirúrgicos. Quanto aos resultados, todos apresentam limitações. A adesão ao tratamento e os casos de recidiva ao longo do tempo representam o maior desafio no controle da doença. Risco cardiovascular aumentado, surgimento de doenças crônicas e uso de medicamentos decorrem do agravamento e evolução da doença. Uma desregulação do tônus muscular palatofaríngeo desempenha um papel significativo nesse distúrbio. Após determinar as melhores condições de irradiação, este estudo teve por objetivo, avaliar o tratamento dos DRS com irradiação sequencial não-ablativa de alta intensidade com dois lasers pulsados: Nd:YAG e Er:YAG (Lightwalker, Fotona), comparando os resultados antes e após a intervenção. Um ensaio clínico controlado, randomizado e duplo-cego foi realizado com aprovação do comitê de ética em pesquisa. Trinta voluntários que transitavam entre ronco primário e apneia obstrutiva do sono moderada foram tratados em três sessões de irradiação laser não-ablativa, com intervalo de 14 dias entre elas. O lúmen de vias aéreas superiores (VAS), para passagem do fluxo aéreo foi analisado por registro fotográfico, de acordo com o índice Mallampati modificado. Parâmetros de dessaturação de oxihemoglobina, gravidade do ronco (amplitude do ruído e tempo de sono com ronco) e qualidade do sono também foram avaliados. O principal resultado clínico obtido é a expansão da luz da via aérea superior pela diminuição da complacência tecidual, em procedimento ambulatorial. Com isso, melhora dos DRS.

Palavras-Chave: Distúrbios respiratórios do sono. Ronco primário. Apneia obstrutiva do sono. Complacência tecidual. Lasers não ablativos de alta intensidade.

ABSTRACT

Primary snoring and obstructive sleep apnea (OSA) represent different severity degrees of the same chronic, complex and progressive disease, which affects about one billion people worldwide. It is more prevalent in elderly men. Historically, snoring is seen as a social problem, being considered the most benign form of sleep breathing disorders (SBD). Because of this, treatment is not prescribed. Snoring noise occurs as a result of soft tissue vibration in the region of upper airway (UA) greater constriction during sleep. Therapeutic options may involve medical treatments, use of devices, and surgical procedures. As for the results, all of them have limitations. Adherence to treatment and cases of relapse over time represent the greatest challenge in disease control. Increased cardiovascular risk, emergence of chronic diseases and use of medications result from worsening and disease progression. A dysregulation of palatopharyngeal muscle tone plays a significant role in this disorder. After determining the best irradiation conditions, this study aims to evaluate the treatment of SBD with high intensity non-ablative irradiation with two pulsed lasers: Nd:YAG laser (1064 nm) followed by Er:YAG laser (2940 nm), both from Fotona LightWalker platform, comparing results before and after the intervention. A controlled, randomized, double-blind clinical trial was performed with approval of the research ethics committee. Thirty volunteers that transitioned between primary snoring and moderate obstructive sleep apnea were treated in three sessions of non-ablative laser irradiation, with a 14-day interval between them. The upper airway lumen for airflow passage was analyzed by photographic record, according to modified Mallampati index. Oxyhemoglobin desaturation parameters, severity of snoring (noise amplitude and sleep time with snoring) as well as aspects of sleep quality were also evaluated. The main clinical result obtained is the expansion of the upper airways lumen by reduction of tissue compliance in an outpatient procedure. Therefore, improvement of sleep breathing disorder.

TABLE LIST

LIST OF FIGURES

LIST OF ACRONYMS, ABBREVIATIONS AND SYMBOLS

δ – is used to designate angles

θ – is used to identify angles

$\approx$ – approximately equal

$>$ – bigger then

$\leq$ – less or equal

$<$ – less than

α – significance

λ – wavelengh

$\geq$ – bigger or equal

α_a – absorption coefficient

μm – micrometers

α_{rd} – reduced dispersion coefficient

μs – microsecond

% – percentage

= – equal

AHI – apnea and hypopnea index

^{o}C – Celsius degrees

AT – adenotonsillectomy

BMI – body mass index

BQ – Berlin questionnaire

CAAE – certificate of approval of ethical appreciation

cal – calorie

CBCT – cone beam computed tomography

CCI – intraclass correlation coefficient test

CCT– controlled clinical trial

CEP – Research Ethics Committee

CNS – central nervous system

CO_2 – carbon dioxide

CPAP – continuous positive air pressure

dB – decibels

E – energy

ECM – extracelular matrix

ED – energy density

EDS – execessive daytime sleepiness

Er,Cr:YSGG – gallium oxide, scandium and yttrium matrix doped with erbium and chromium

ER:YAG – yttrium-aluminum-garnet matrix doped with erbium

ESS – Epworth sleepiness scale

eV – electron-volt

f – fluence

f_{abl} – ablation fluence

FOUSP – University of São Paulo School Dentistry

HGNS – hypoglossal nerve stimulation

HSP – heat shock protein

Hz – Hertz

ICF – Informed consent form

IPEN – Nuclear and Energy Research Institute

J – Joule

Kg/M^2 – measure unit of mass in kilograms per square meter

L – laser optical penetration depth

LP – long pulse

MAD – mandibular advancement dispositive

mm – millimetres

MMA – maxillomandibular advancement

MMP2 – matrix metalloproteinase-2

ms – millisecond

N – number of research participants

ND:YAG – yttrium-aluminum-garnet matrix dopaed with neodymium

nm – nanometers

OA – oral appliance

ODI – oxyhemoglobin desaturation index

OR – odds ratio

OSA – obstructive sleep apnea

P – power

p – represents the value that corresponds to the probability of the detected difference having occurred by chance

PD – power density

PS – primary snoring

PSG – polysomnography

PSQI – Pittsburgh sleep quality index

RCT – randomized controlled trial

RDI – respiratory disturbance index

RF – radiofrequency

ROS – reactive oxygen species

s – second

SAH – systemic arterial hypertension

SBD – sleep breathing disorder

t – time

TE – tonsillectomy

T_{exp} – exposure time

TGF β1 – Transforming growth factor – beta one

T_{r} – thermal relaxation time

UA – upper airway

UARS – upper airway resistance syndrome

UPPP – uvulopalatopharyngoplasty

UV – ultravioleta energy

VAS – visual analogic scale

VHS – variable heat shock

W – Watt

W/cm^2 – measure unit of watt per square meter

Wnt1 – a fibroblast lineage

SUMMARY

1 INTRODUCTION

1 INTRODUCTION

1.1 Sleep

Sleep is an active physiological process, essential for organism balance and responsible for body homeostasis maintenance. Restricting the number of hours, as well as compromising sleep quality, can lead to sleep disorders. Among these disorders, one group stands out for its high prevalence in population: the sleep breathing disorders (SBD), widely recognized throughout society but poorly understood as one of the main causes of various cardiovascular and metabolic diseases, affecting about one billion people worldwide with 33% prevalence in adult population of São Paulo city. According to data from the Brazilian Sleep Association, 36.5% of Brazilians sleep poorly. From 1960 to 2012, the average duration of sleep time decreased by more than 18%.[1-5]

1.2 Sleep breathing disorders

Due to its multiple functions, pharynx must be both flexible to facilitate speech and swallowing, and rigid to maintain airflow during breathing. Upper airway (UA) patency is maintained predominantly by the action of pharyngeal muscles. Negative pressure within the airway generated on inspiration and the positive pressure around the airway (due to the accumulation of adipose tissue and craniofacial conformation) tend to promote its collapse. During sleep, there is a reduction in pharyngeal muscles tone, which even in normal individuals, causes narrowing of the lumen and increased airway resistance.[6-16]

Figure 1 – Balance of forces in the neuromechanical control of upper airway patency during sleep.
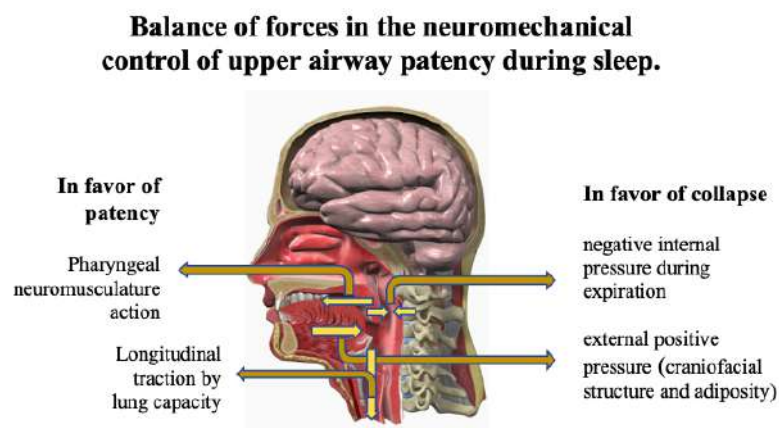
Balance of forces in the neuromechanical control of upper airway patency during sleep.

In favor of patency
Pharyngeal neuromusculature action
Longitudinal traction by lung capacity

In favor of collapse
negative internal pressure during expiration
external positive pressure (craniofacial structure and adiposity)

24

Sleep breathing disorder (SBD) is a chronic, complex and progressive condition whose main clinical sign is the loud and frequent snoring. According to the literature, the main risk factors are obesity and advancing age. Upper airway obstruction of multifactorial origin is its main pathophysiology, involving structural anatomical characteristics, muscle response, awakening threshold and also loop gain, but with different severity degrees. Respiratory impairment, sleep disruption and increased daytime sleepiness result from worsening and evolution of the disease, as a result of repetitive and prolonged vibration of pharyngeal structures during respiratory events, leading to a polyneuropathy over time, in the trauma presence.[16,17]

Thus, imbalance in muscle tone that sustains the pharyngeal lumen during sleep is established. Decreased airflow to lungs and breathing interruptions result in less blood oxygenation. Drop in saturation levels causes an excitation of the central nervous system (CNS) with release of catecholamines and stimulation of the cardiovascular system to increase sympathetic system tone, promoting cortical arousal. The individual wakes up, ceasing the event, with respiratory flow reestablishment. A cascade activation of alterations in metabolism also occurs with serious hemodynamic, neurological and behavioral repercussions. Clinically, an increase in heart rate and blood pressure can be observed, thus establishing the basis for emergence and/or worsening of hypertension, atherosclerosis, type II diabetes and obesity.[16-19]

Figure 2 – Schematic outlining proposed pathophysiological components of obstructive sleep apnea (OSA), activation of cardiovascular disease mechanisms and consequent development of established cardiovascular disease.
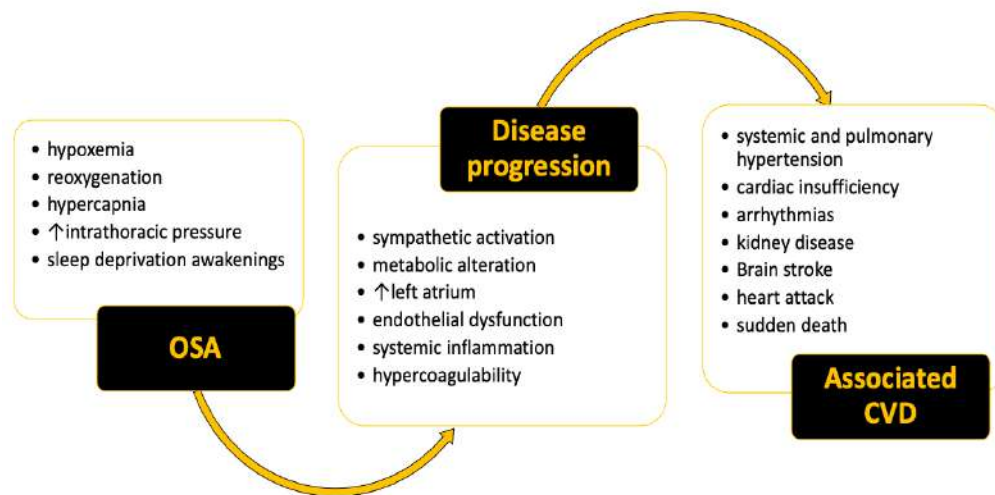
Understanding the increased risk for comorbidities underscores the importance of early diagnosis and effective management. [20-22]

Sleep breathing disorders are presented according to severity, in:

- Primary snoring (PS): occurs when oxyhemoglobin desaturation index (ODI) is less than 5 events per hour of sleep, in absence of sleep deprivation symptoms;
- Upper airway resistance syndrome (UARS): ODI less than 5 events per hour of sleep, but respiratory effort and arousal occur without characterizing hypopnea or apnea, in presence of sleep deprivation symptoms, such as excessive daytime sleepiness;
- Hypopnea: is 30% airflow reduction in presence of respiratory effort and 4% drop in saturation or 30% airflow reduction, associated with 3% drop in saturation and awakening;
- Apnea: may be of central, obstructive, or mixed origin. Presence or absence of respiratory effort is the main difference. Other criteria are the same for all three types, involving a 90% airflow drop for at least ten seconds. It can be classified into:
  - Light OSA: ODI between 5 and 15 events per hour;
  - Moderate OSA: ODI between 15 and 30 events per hour;
  - Severe OSA: ODI above 30 events per hour.[1,2,5,20]

Figure 3 – Illustrative pharynx diagram during normal breathing, with partial obstruction and production of snoring and, total obstruction and obstructive sleep apnea.

Normal breathing **Snoring** **Obstructive sleep apnea**

Dra. Valeria Mendes CRO: 56.166
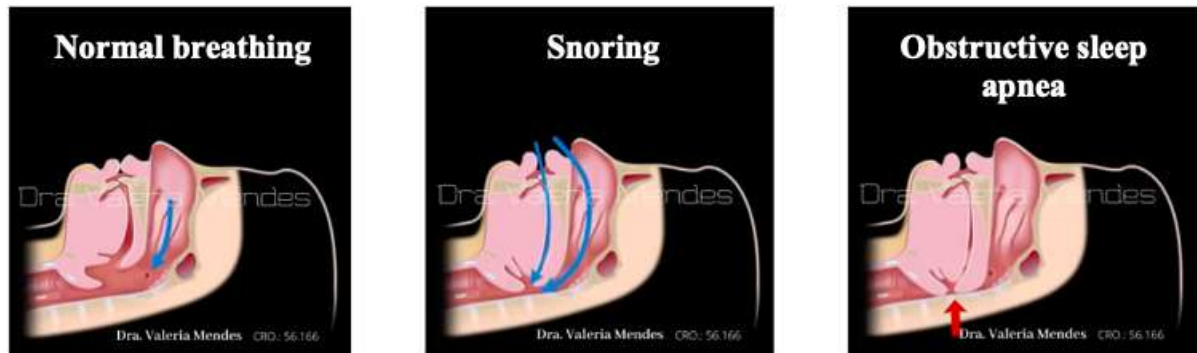
Source: Personal archive of the dissertation author. License obtained from Alila Medical Media for Valeria Mendes no. O-2102202001132

Historically, snoring has been seen as a social problem and is considered the most benign form of sleep-disordered breathing. Because of this, treatment is not prescribed. The progression from normal nocturnal breathing to snoring and OSA involves increased sagging in the upper airways, especially in the lateral pharyngeal wall.

Aging plays an important role in the progressive increase in upper airway (UA) compliance, with consequent increase in predisposition to collapse, leading to an increase in OSA prevalence. The determining factors of skeletal muscle compliance are not known, but in patients with snoring and OSA, the pharynx is narrower and more collapsing. At any stage of this complex and progressive disease, proper diagnosis and treatment are important.[6,7,17-20]

Figure 4 – Snoring and tissue compliance in a feedback relationship.
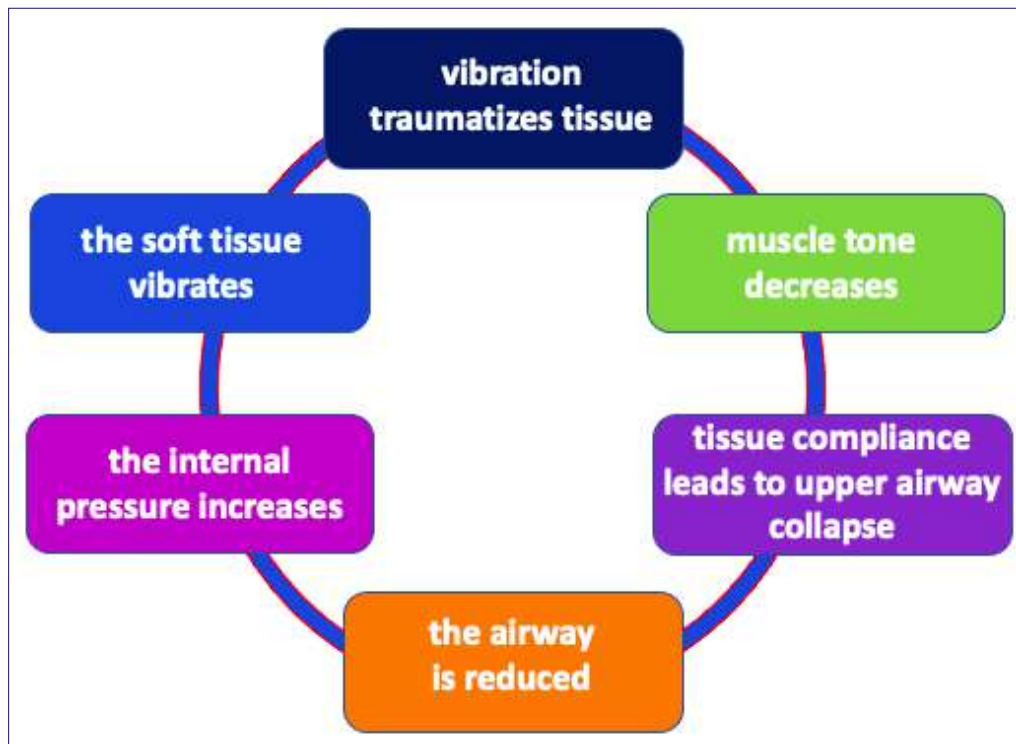
Source: personal file of the author of this dissertation

Diagnosis is medical. Based on clinical history, detailed physical examination and polysomnography exam, according to the AHI value, that is the number of obstructive respiratory events per hour of sleep, resulting in blood oxygen or oxyhemoglobin desaturation. To understand the clinical history, type I polysomnography (PSG I), performed in the laboratory, under technical supervision, is the gold standard test. However, given resource limitations including limited number of registration beds, high cost, long waiting lists, and need for manpower, many authors have explored the use of clinical predictors (such as modified Mallampati index, intensity of symptoms, impact on social life and professional functions, in addition to presence of cardiovascular diseases) or sleep questionnaires, which can help identify patients at higher risk.[1,2,5,8,22-28]

Screening devices like single or multi-channel monitoring systems have also been introduced and may represent an alternative method for diagnosing OSA. This study used type IV polysomnography, which uses high-resolution oximetry to obtain outcome measures. Therefore, we will always use the oxyhemoglobin desaturation index (ODI) as a parameter for the evaluation of sleep breathing disorder. According to the American Academy of Sleep Medicine, a minimum drop of 3% to 4% in oxyhemoglobin saturation is a criterion for defining hypopnea. Thus, the Apnea and Hypopnea Index (AHI) and the Oxyhemoglobin

Desaturation Index (ODI), used to grade the severity of SBD, are strongly correlated in accuracy, sensitivity and specificity, fact proven in a study published in 2020.[29,30]

For outpatient physical examination, the methods most correlated with predicting severity of obstructive sleep apnea are modified Mallampati classification and Friedman tongue position assessment techniques, according to the systematic review and meta-analysis published in Jama Otolaryngology Head Neck Surgery in 2013.[24,25]

Mallampati classification system is visualized with the tongue protruding and was initially developed to predict the ease of patients intubation and later, adapted by sleep medicine as a method of assessing severity of sleep breathing disorder in outpatient setting and also to predict indication of airway surgery according to relationship between different structures; tongue size in relation to uvula, tonsils, soft palate and oropharyngeal walls.[1]

Figure 5 – Mallampati classification.
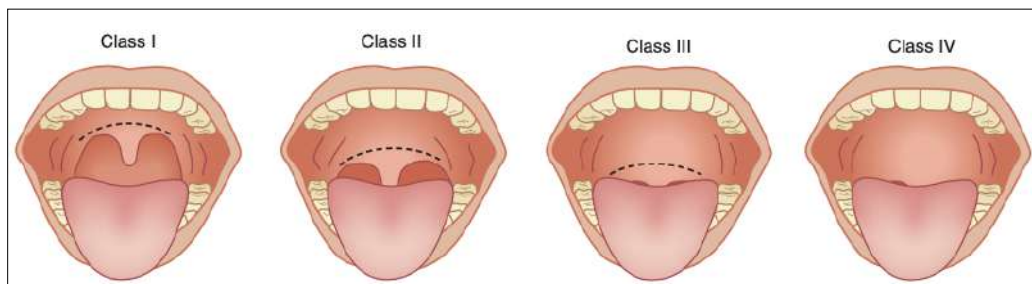
Source: Kryger MH, Roth T, Dement WC. Principles and practice of sleep medicine. 4. ed. Philadelphia: WB Saunders, 2005.

Modified form of Mallampati classification system is performed with tongue positioned on mouth floor and has greater similarity to physiological resting position found during sleep. The modified form is validated as a predictor of obstructive sleep apnea severity:

- Class I — entire posterior wall of oropharynx is visualized, including inferior pole of palatine tonsils;
- Class II — part of posterior wall of oropharynx is visualized;
- Class III —insertion of uvula and soft palate are visualized, and posterior wall of oropharynx cannot be seen;
- Class IV — only a part of soft palate and hard palate are visualized.[24]

Figure 6 – Adaptation for sleep breathing disorders (SBD) assessment: modified Mallampati index.
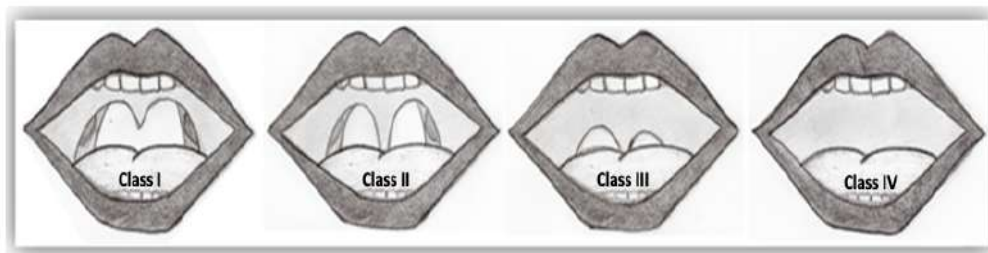
Source: personal file of the author of this dissertation

Oropharynx and oral cavity of OSA individuals have higher prevalence of thick posteriorized soft palate, median tonsillar pillars, long and thick uvula, absent palatine tonsils, bulky tongue and modified Mallampati, grades III or IV, considered unfavorable. Mallampati modified grades III or IV and increased neck circumference showed good sensitivity and may be useful for OSA screening, according to a study published by Maria Claudia Soares in 2015.[25]

As a clinical history investigation tool, sleep questionnaires are quite useful.

Pittsburgh Sleep Quality Index (PSQI) assesses sleep quality and disturbances over a one-month period, being a valuable tool for research purposes. A 2012 publication in Sleep Medicine demonstrates PSQI-BR is a valid and reliable instrument for assessing sleep quality, being equivalent to its original version when applied to individuals who speak Portuguese in Brazil. Despite relevant cultural and linguistic influences, no major cultural adaptations were necessary during the validation process.

Epworth Sleepiness Scale (ESS) was developed based on observations of nature and occurrence of daytime sleepiness, assessing the likelihood of falling asleep in eight situations involving daily activities, some of which are known to be highly sleepy. Global score ranges from 0 to 24. Scores greater than 10 suggest diagnosis of excessive daytime sleepiness (EDS). ESS was translated and validated for use in Brazilian Portuguese, being a valid and reliable instrument for assessing daytime sleepiness, equivalent to its original version, widely used because it is simple, easy to understand and quick to fill.

Berlin Questionnaire (BQ), a screening tool for obstructive sleep apnea (OSA) in primary care, has but been applied in tertiary settings, with variable results. Article published in 2011-Pneumology Portuguese Journal, developed the Portuguese version of BQ and validated its use in a sleep breathing disorder (SBD) clinic. According to publication, BQ is not an adequate screening tool for OSA, but for snoring intensity, witnessed apnea, systemic arterial hypertension (SAH)/obesity were significant.[26-28]

In the Sleep Heart and Health Study, a positive association between OSA severity and occurrence of stroke was detected. According to the publication, each 1-unit increase in AHI resulted in a 6% increase in risk of having a stroke. Another study showed severe cases of OSA were associated with a 3-fold increased risk of cardiovascular events. In 2016, Ando S. published hypertension is one of the most prevalent diseases in the world and has been shown to be closely related to sleep-disordered breathing (SDB), which influences blood pressure through several pathways, including sympathetic nervous system activation and hormonal or endothelial dysfunction. In 2018, Khazaie H and colleagues concluded while sleep apnea plays an important role in hypertension, data demonstrate snoring is also a risk factor for hypertension independent of BMI, AHI, and age. Because snoring is an easily detectable acoustic signal, early identification and adequate management could reduce cardiovascular risk, a strategy indicated to reduce hypertension associated with snoring and sleep apnea in the population. Likewise, OSA is known to be related to dysregulation of immune system.[6,16,19,31-36]

Thus, the objective of treatment is to restore upper airway patency, stabilizing nocturnal ventilation and oxygenation, with snoring and sleep fragmentation correction. Best approach choice is based on several factors that determine patient phenotype, such as SBD severity, minimal oxygen saturation during sleep, presence of comorbidities, and not just on the absolute number of apneas and hypopneas. [1,2,4,7,19,22]

Individualized therapeutic approach takes into account the patient phenotype and according to 4Ps, can:

- Predict – who is at greatest risk of developing disease and comorbidities;
- **Prevent – aims to prevent the disease development;**
- Personalize – individualized proposals for both, diagnosis and treatment;
- Participate – patient actively participates in health care.[37]

Treatment modalities involve elimination of alcohol, establishment of healthy habits, exercise and controlled diet. There are options including positional therapy, medication use, mandibular advancement devices, nasal clips, myofunctional therapies or even a positive pressure device (CPAP), gold-standard treatment for OSA, which acts through the application of positive pressure from a device that generates a constant air flow in upper airways, to keep pharynx open during sleep. Surgical and invasive procedures such as palatal implants,

uvulopalatopharyngoplasty (UPPP) and uvulopalatoplasty are sometimes indicated, and other times rejected by patients due to hospitalization, anesthesia, pain and significant postoperative discomfort. Most procedures have limitations. There are also cases of recurrence, even after surgery. Non-adherence to therapy by patients happens frequently.[16,20,38-51]

Figure 7 – Treatment for OSA with continuous positive air pressure (CPAP).
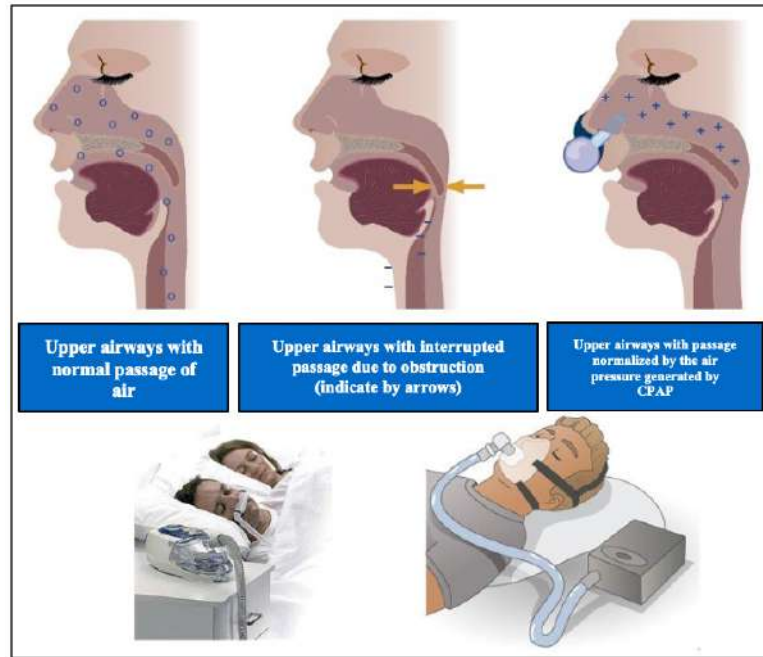
Source: OSA Treatment Workbook – Positive Pressure. Postgraduate HIAE Sleep Course and adapted for presentation in this study.

According to Xia F. publication in 2021, success rate of CPAP therapy is 59.3%, but it has poor adherence to treatment, mandibular advancement intraoral appliance is 68% but can cause occlusal problems, weight loss, 27% but difficult to achieve and maintain, maxillomandibular advancement surgery, 27.6% but it is a complex and highly invasive procedure with immediate side effects such as hemorrhage, risk of infection and malocclusion. Uvulopalatopharyngoplasty (UPPP), which promotes excision of the upper airways compliant tissue, has a 44.35% success rate, but an increased risk of velopharyngeal insufficiency and dysphagia. When combined with tonsillectomy, the rate rises to 64.5% but limitations remain the same. Adenotonsillectomy, 27.2% and is accompanied by bleeding and risk of infection in postoperative period. Implantation to stimulate the genioglossus, 77 .1%, but it has a high cost, can malfunction and causes abnormal sensations such as burning on the tongue.[51]

Table 1 – Success rate and limitations of treatments for obstructive sleep apnea (OSA).

Methods / Limitation	Non-Invasive Methods			Invasive Methods				
	CPAP [53]	OA [58]	Weight Loss [83]	MMA [101]	UPPP [94]	UPPP+TE [98]	AT [106]	HGNS [117]
Severity of OSA	Mild-severe	Mild-severe	Mild-severe	Severe	Moderate-severe	Moderate-severe	Moderate-severe	Severe
Number of samples	463	425	132	29	212	31	578	584
Pre(mean)	48.6 ± 31.8	27.5 ± 16.3	27.6 ± 24.6	36.7 ± 14 (S)	39.9 ± 18.3	33.7 ± 14.6	18.2 ± 21.4	33.8 ± 15.5
Post(mean)	5.7 ± 8.4	12 ± 12.5	9.9 ± 11.2	4.7 ± 3.2 (S)	21.5 ± 15.6	15.4 ± 14.1	4.1 ± 6.4	11 ± 13.6
AHI < 5 or AHI reduction > 50%	59.3%	68%	27%	27.6%	44.35%	64.5%		77.1%
AHI < 1							27.2%	
Follow-up	7 years	4 years	1 year	12.5 ± 3.5 years	≥34 months	3 months	Immediately	1 year
Efficiency	+++++	+++	+	+++++	+++	++++	++	+++++
Limitations	Poor adherence	Strict teeth structure, long-term overjet and overbite	Difficult to achieve weight loss and maintain	Highly invasive and complicated procedure, side effects include malocclusion, hemorrhage, facial numbness, etc.	Velopharyngeal insufficiency, dysphagia, swallow difficulty	Velopharyngeal insufficiency, dysphagia, swallow difficulty	Post-operative bleeding, infection of wound	High cost, tongue abrasion, device malfunction, abnormal sensations, etc.

CPAP, continuous positive airway pressure; OA, oral appliance; MMA, maxillomandibular advancement; UPPP, uvulopalatopharyngo-plasty; AT, adenotonsillectomy; TE, tonsillectomy; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; HGNS, hypoglossal nerve stimulation; Pre(mean) is the mean AHI value before treatment; Post(mean) is the mean AHI value after treatment. More '+' sign means the higher treatment outcome.

Source: Xia F., Sawan M. Clinical and Research Solutions to Manage Obstructive Sleep Apnea: A Review. Sensors. 2021;21:1784.

Katia C Guimarães and colleagues published in the American Journal of Respiratory and Critical Care Medicine, 2009, that oropharyngeal exercises significantly reduce severity and symptoms of OSA, representing a promising treatment for the moderate cases, as they obtained a 39% reduction in AHI value.[48]

In 2010, Valbuza et al performed a systematic review including controlled clinical trials that used methods to improve muscle tone on UA, with an AHI result of less than five events per hour as main outcome, and found no evidence of efficacy in the UA therapeutic proposal. [49]

Aging is a physiological phenomenon that involves loss of cellular regeneration capacity. The maintenance of tissue architecture and physiology is attributed to extracellular matrix, with its collagen and elastic fibers, responsible for tissue resistance and elasticity, synthesized by fibroblasts. With aging, collagen fibers, central components of connective tissue, gradually become stiffer (type I collagen increases and type III collagen decreases). Type l gives strength, type lll more elasticity. Elastin, another component of connective tissue, also gradually loses its natural elasticity.[53-61]

Many alternatives are available to restore and/or increase collagen, remodeling the tissue, improving sagging, such as laser treatments, which are quite popular in dentistry and aesthetics. Non-invasive and non-ablative laser treatment for sleep breathing disorder aims to improve muscle tone, remodeling tissue to increase oropharyngeal space, facilitating the airflow passage.[62,63]

According to Resolution nº 82, of the Federal Council of Dentistry, of September 25th, 2008, laser therapy qualified dentists have the face as field of action, for diagnosis and treatment of pathologies that encompass maxillary-mandibular complex, the lower limit being hyoid bone.[64]

2 OBJECTIVES

2 OBJECTIVES

After determining the best irradiation conditions, this study aimed to clinically evaluate the effect of non-ablative treatment with association of two high-intensity pulsed lasers, Nd:YAG and Er:YAG, on sleep breathing disorder (SBD) through analysis of the upper airway lumen (UA), comparing results before and after intervention.

2.1 Specific Objectives

- Evaluate and compare oxyhemoglobin desaturation index (ODI), minimum and mean oxyhemoglobin saturation during sleep, as well as saturation time below 90%, for each participant, at beginning and the end of treatment;
- Assess the impact of laser treatment on noise amplitude and snoring time during sleep, comparing pre and post-treatment records.
- Analyze the perception of the laser intervention effectiveness, by research participants, through application of questionnaires addressing snoring complaints, daytime sleepiness and sleep quality, comparing results before and after the intervention.

2.2 Rationale

Due to high prevalence of snoring and OSA, complexity and morbidity of the disease, low adherence/acceptance to CPAP and limited response of other therapeutic options described in literature, new treatment options that can be adopted are still necessary, as a first step choice or as a combined therapy. Myofunctional exercises proposed in speech therapy require patient adherence to therapeutic proposal, in addition to assiduity in execution, for a long time. However, they reveal positive evidence that oropharynx improved muscle tone contributes to reducing snoring and OSA severity. This fact points to promoting improvement in oropharyngeal muscle tone possibility through non-ablative treatment with high-intensity pulsed lasers, representing a new therapeutic approach, which does not require anesthesia or hospitalization, indicated for cases of non-adherence to standard therapy or as combined therapy.[48-64]

In a macro-scenario view, the current supplementary health market points to a strong trend towards verticalization of operations to manage costs. With life expectancy increasing, effective preventive actions for high prevalence chronic diseases control, such as arterial hypertension and type II diabetes, resulting from the worsening and progression of SBD, that can be carried out in few outpatient sessions, certainly would represent an important economy for health organizations around the world. This study is needed to confirm the benefits of this treatment for sleep breathing disorder approach.

The Nuclear and Energy Research Institute (IPEN) is a reference center and offers a suitable environment for studies and research on radiation technologies in health sciences. Thus, dental care in sleep breathing disorder patient management will bring a great benefit to society, to patient quality of life, to health costs management, in addition to contributing to the continuing education process in a multidisciplinary team.

3 STUDY HYPOTHESIS

3 STUDY HYPOTHESIS

This study hypothesis is that non-ablative treatment of sleep breathing disorder with combination of two high-intensity pulsed lasers, Nd:YAG and Er:YAG is capable of reducing tissue compliance in oropharynx, with consequent upper airways space increase, facilitating airflow passage for breathing and consequent decreasing in oxyhemoglobin desaturation rates, saturation time below 90% and improvement of oxyhemoglobin saturation parameters during sleep. In addition, decrease in noise amplitude and snoring time during sleep is expected, improving in patient quality of sleep, with good intervention acceptance.

4 LITERATURE REVIEW

4 LITERATURE REVIEW

4.1 Publications on use of lasers in the treatment of sleep breathing disorder (SBD)

Keywords and Boolean operators used in publications search were: (snoring) OR (snore) OR (sleep apnea) OR (sleep disorder) OR (obstructive sleep apnea) OR (obstructive sleep apnea syndrome) AND (laser) OR (non-ablative laser) OR (Er:YAG laser) OR (nightlaser) OR (laser therapy). Query was performed in the following databases: Web of Science, Pubmed, Embase, Scielo and Google Scholar.

Inclusion criteria were: case-control studies, retrospective and prospective cohort studies, systematic and meta-analyses published in English and with availability of access to full text. Sixteen articles were selected: one systematic review and meta-analysis, thirteen case series and two randomized clinical trials. The main notes of each publication were:

Author, year, country and title	Dovsak D, Gabrijelcic J, Vizintin Z 2011, Slovenia NightLaseTM – a new laser treatment method for reducing snoring and sleep apnea – a pilot study. J Laser Health Acad 1:9–10
Study design	Case series, prospective study
Study N, use of control group	11; no control group
Diagnosis	no information
Age and gender	no information
Inclusion criteria	no information
Exclusion criteria	no information
Irradiated region	no information
Outcome measures	Snoring duration time; respiratory disorder index(RDI) in polysomnography and application of questionnaires, before, one month and three months after treatment.
Results	Improvement of 23% for snoring and 30% for general improvement in sleep assessed by questionnaire; RDI improved in 4 patients. On polysomnography, 2 patients had extremely low measured snoring times (0.6 min and 1.0 min), indicating very high variability in night-to-night snoring or possible measurement error. Among the remaining 9 patients, one had no changes, five had a reduction in snoring duration ranging from 9% to 100% and three patients had an increase in snoring duration. The mean reduction in snoring duration measured for these nine patients was 11%.
Follow-up time	03 months.
Complications	No adverse effects

Laser type, wavelength, emission mode	Laser Er:YAG; : 2940 nm; pulsed mode
Operation mode	Mention only Night Lase_{MT} treatment
Average power	No information
Point diameter	No information
Source-tissue distance	No information
Repetition rate	No information
Energy and pulse width	No information
Energy density	No information
Number of pulses, number of treatment sessions, interval between sessions	No information Two-session treatment; Does not mention the interval between them

Author, year, country and title	Jovanovic J 2011; Bosnia and Herzegovina NightLaseTM – laser –assisted snoring and apnea reduction, 9 months of experience. J Laser Health Acad 1:11
Study design	Case series, prospective study
Study N, use of control group	21
Diagnosis	No information
Age and gender	No gender information; age between 26 and 59 years
Inclusion criteria	age between 26 and 59 years
Exclusion criteria	No information
Irradiated region	Only cites soft intraoral tissue
Outcome measures	application of questionnaires
Results	Although the study reported 3 treatment sessions, the result shown was after the first and second sessions: a mean of 62% improvement in reported snoring reduction and 68% improvement in total sleep score.
Follow-up time	No information
Complications	None of the treated patients had pain or discomfort during treatment.
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) Pulsed emission mode
Operation mode	It only quotes NightLaseMT; with 8 laser scans in each region followed by 4 strategic passes.
Average power	No information
Point diameter	No information
Source-tissue distance	No information
Repetition rate	No information
Energy and pulse width	No information
Energy density	No information
Number of pulses, number of treatment sessions, interval between sessions	Three sessions (days 1, 15 and 45) with intervals of 14 and 30 days, respectively

Author, year, country and title	Miracki K, Vizintin Z 2013; Poland and Slovenia Nonsurgical minimally invasive Er:YAG laser snoring treatment. J Laser Health Acad 1:36–41
Study design	Case series, retrospective study
Study N, use of control group	57
Diagnosis	Snoring and other sleep breathing disorders
Age and gender	Age between 27 and 74 years; 47 men and 10 women
Inclusion criteria	No information
Exclusion criteria	Patients using photosensitive drugs and pregnant women.
Irradiated region	Anterior pillar extending from the external face to the retromolar region and posterior third of the cheek (two regions – one left and one right); the soft palate and the uvula with the lower part of the hard palate (two symmetrical regions); the posterior pillars and tonsils (two regions); the lateral and inferior sides of the tongue (also two regions).
Outcome measures	Snoring questionnaire during follow-ups at 14 days and 45 days; Mallampati index
Results	The average snoring severity score improved by 50%; the average total SBD score improved by 44.9% 79.6% of patients expressed satisfaction with the treatment. 74% of patients reported improvement, while 26% of patients reported no changes after treatment. 57.1% showed significant improvement in snoring.
Follow-up time	15 months after the end of treatment, by telephone contact
Complications	Only mild discomfort during treatment was recorded, and there were no other adverse effects.
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) (SP Dualis, Fotona, Slovenia) Pulsed emission mode
Operation mode	Quote according to laser parameters and treatment protocol as per manufacturer proprietary description
Average power	No information
Point diameter	Quote only PS03 handpiece with standardized beam
Source-tissue distance	It only says contactless mode
Repetition rate	No information
Energy and pulse width	No information
Energy density	No information
Number of pulses, number of treatment sessions, interval between sessions	It cites coverage of the regions defined in the so-called manual brushing technique. 3 sessions, with intervals of 14 and 45 days, respectively.

Author, year, country and title	Svahnström K 2013; Sweden Er:YAG laser treatment of sleep-disordered breathing. J Laser Health Acad 2:13–16

Study design	Case series, retrospective study
Study N, use of control group	117 but after exclusion criteria, 75; no control group
Diagnosis	Different degrees of snoring and obstructive sleep apnea
Age and gender	No information
Inclusion criteria	No information
Exclusion criteria	Photosensitive drugs, pregnancy, narrow throat, fear, obesity, very high expectations, illness, and being a minor. Patients with pollen allergy were treated after the season ended.
Irradiated region	Anterior pillar, soft palate and uvula with underside of hard palate, posterior pillars and tonsils, lateral and fundus of tongue.
Outcome measures	Mallampati classification; report of patients and partners about satisfaction, by questionnaires.
Results	Result by Mallampati index only after treatment, without baseline reference. 21 class IV patients; 36 (class 3); 16 (class 2) and 2 (class 1). The success rate per questionnaire was 90%. Of the total number of patients, 33% (25) reported being very satisfied, 44% (33) satisfied and 13% (10) reported being somehow satisfied with the treatment. More than 80% of patients also reported that they were able to breathe much more easily after treatment, becoming more alert and focused. They also noticed that their gag reflexes were decreased, that they had no more pressure related problems when flying, fewer headaches, and they also noticed better sex and felt more confident, etc. Regarding blood oxygenation, in general there was no significant difference in the amount of oxygen in the blood before and after treatment.
Follow-up time	six to twelve months
Complications	No side effects or risk to patients
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) (LightWalker AT, Fotona, Slovenia); Pulsed emission mode
Operation mode	It says treatment protocol and manufacturer parameters were followed and that the procedure was stopped when mucosal retraction was observed.
Average power	No information
Point diameter	It says PS04 handpiece with a patterned beam
Source-tissue distance	It only says contactless mode
Repetition rate	No information
Energy and pulse width	No information
Energy density	No information
Number of pulses, number of treatment sessions, interval between sessions	The number of treatment pulses administered per patient depended on the person anatomy, ranging from 12,000 to 17,000. Three sessions were performed in a period of 45 days. It does not mention the interval between treatment sessions.

Author, year, country and title	Sippus J 2015; Finland Case report: NightLaseR procedure- laser snoring and sleep apnea reduction treatment. J Laser Health Acad 1:1–5
Study design	Case series, retrospective study
Study N, use of control group	10; no control group
Diagnosis	Different levels of OSA
Age and gender	No information
Inclusion criteria	No information
Exclusion criteria	No information
Irradiated region	It only says soft intraoral tissue
Outcome measures	Mallampati classification; patient reports for snoring
Results	After the third treatment, patients reported an improvement in snoring greater than 85%, after the second, 61%, and after the first, 51%. It showed five cases of Mallampati grade IV that after treatment could be classified as grade I
Follow-up time	28 to 36 months
Complications	Easy treatment to perform, no pain during or after treatment.
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) (LightWalker AT, Fotona, Slovenia); Pulsed emission mode
Operation mode	Long pulse (LP) mode, the laser beam is manually delivered through the target, vertically or horizontally (depending on the region), multiple passes are performed in each region (with well-defined overlap)
Average power	No information
Point diameter	It just says HP PS04 handpiece in minimally invasive configurations per manufacturer protocol
Source-tissue distance	No information
Repetition rate	10 Hz
Energy and pulse width	No information
Energy density	No information
Number of pulses, number of treatment sessions, interval between sessions	Total pulses delivered varies per patient between 10,000-15,000. Three treatment sessions were made. Cites that sessions are scheduled at appropriate time intervals

Author, year, country and title	Lee CYS, Lee CCY 2015; USA Evaluation of a non-ablative Er:YAG laser procedure to increase oropharyngeal airway volume: a pilot study. Craniofac Oral Dent 1:56–59
Study design	Case series, prospective study

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Study N, use of control group	7
Diagnosis	Primary snoring and OSA of different degrees
Age and gender	Mean age of 59.5 years; 5 men and 2 women
Inclusion criteria	No information
Exclusion criteria	No information
Irradiated region	Palatoglossal arch, palatopharyngeal arch, and uvula
Outcome measures	CBCT (pharyngeal airway volume and minimum cross-sectional area – most constricted values), statistical analysis by paired t test and p < 0.05
Results	The total volume of the airways increased by 22.6% and the minimum constricted area, by 29.8%, with p = 0.0179
Follow-up time	Approximately 12 weeks after laser treatment.
Complications	No information
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) Pulsed emission mode
Operation mode	Variable Pulse Laser Mode; 6 shots per point with overlap
Average power	3 W
Point diameter	The laser beam spot size is 10.0 mm
Source-tissue distance	approx. 20.0 to 25.0 mm away from the target tissue
Repetition rate	6 Hz
Energy and pulse width	500 mJ
Energy density	No information
Number of pulses, number of treatment sessions, interval between sessions	Four sessions with a two-week interval between sessions

Author, year, country and title	Unver T, Aytugar E, Ozturan O, Kıran T, Ademci E, Usumez A. 2016; Turkey Histological Effects of Er:YAG Laser Irradiation with Snoring Handpiece in the Rat Soft Palate. Photomed Laser Surg. 2016
Study design	Controlled, randomized clinical trial; prospective
Study N, use of control group	20
Diagnosis	Not applicable
Age and gender	Adult Wistar albino rats weighing 200-250 g
Inclusion criteria	Not applicable
Exclusion criteria	Not applicable
Irradiated region	soft palate of mice
Outcome measures	Histological analysis of the rat palate removed by biopsy, with statistical analysis by Mann-Whitney U and Spear-man's rho test and p < 0.05.
Results	The overlying mucosa of each mouse in the experimental group was intact with some superficial bleaching, with no sign of tissue charring. All animals recovered normally and tolerated normal food and water intake within 1 to

	1.5 h after resuscitation from anesthesia without further complications. There was no open wound, bleeding or necrosis when the soft palate was macroscopically observed after the animals were sacrificed. Histopathologically, a submucosal thermal effect was observed at 0.4 – 1.7 mm depth, but most of the epithelial tissue was preserved. Inflammatory changes were observed histologically at 3 weeks postoperatively. On the first day of the experiment, the inflammation was classified as grade 2 and remained at the same level during the first week of the procedure. By the third week the inflammation had decreased to 1.3 and by the end of the fifth week it had completely disappeared. Keratinization appeared after the procedure in both groups, but more visibly in the study group.
Follow-up time	Five weeks
Complications	Not applicable
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) Pulsed emission mode
Operation mode	No information
Average power	1,15 W
Point diameter	handpiece for snoring (PS04); 7 mm
Source-tissue distance	Quote only contactless mode
Repetition rate	2 Hz
Energy and pulse width	No information
Energy density	1,5 J/cm^2
Number of pulses, number of treatment sessions, interval between sessions	One intervention, 2-minute irradiation of the soft palate region

Author, year, country and title	Cetinkaya EA, Turker M, Kiraz K, Gulkesen HK 2016, Turkey Er:YAG laser treatment of simple snorers in an outpatient setting. ENT J Ratio Otorhinolaryngol Specification 78:70–76
Study design	Case series, retrospective study
Study N, use of control group	33
Diagnosis	Loud snoring and daytime sleepiness on polysomnography
Age and gender	28 to 70 years; 25 men and 8 women
Inclusion criteria	Age over 18 years, primary snoring (AHI < 5)
Exclusion criteria	In use of photosensitive drugs, pregnancy, any other simultaneous surgical treatment that could affect snoring and body mass index > 25, nasal obstruction, BMI > 25.
Irradiated region	Soft palate, distal portion of hard palate, anterior and posterior pillars, uvula, tonsils, lateral and belly of tongue
Outcome measures	Application of questionnaires; previously observed the

	Mallampati index, but did not use it as an outcome measure.
Results	Results of questionnaires with statistical difference after treatment; between the groups, the one with patients aged 50 to 70 years was different;
Follow-up time	No information
Complications	Mild pain, no need for anesthesia. Light and transient sensation of altered sensation on the palate; dry throat.
Laser type, wavelength, emission mode	Laser Er:YAG; : 2940 nm; Pulsed emission mode
Operation mode	It only mentions Night LaseMT treatment; the procedure was interrupted when mucosal retraction was observed
Average power	No information
Point diameter	It says just PS03
Source-tissue distance	It says just no contact
Repetition rate	No information
Energy and pulse width	No information
Energy density	No information
Number of pulses, number of treatment sessions, interval between sessions	12,000 to 17,000 pulses; 03 treatment sessions: day 0, day 14 and day 42 14 and 28 days apart, respectively

Author, year, country and title	Janjic M 2018; Australia NightLase® Smooth Mode J. LAHA, Vol. 2018, No. 1; P. CB01.
Study design	Case report, prospective study.
Study N, use of control group	1
Diagnosis	Snoring and mild OSA
Age and gender	70 years; men
Inclusion criteria	No information
Exclusion criteria	No information
Irradiated region	No information
Outcome measures	Snorelab; Mallampati classification
Results	Report of significant reduction of snoring, improvement of sleep quality. Mallampati classification from IV to II.
Follow-up time	Five weeks after the end of treatment
Complications	Uneventfully
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) Pulsed emission mode
Operation mode	Smooth mode, 4 to 6 shots per point, no overlap; with 4 to 6 laser scans
Average power	No information
Point diameter	R11 handpiece with 7 mm diameter at the point
Source-tissue distance	No information
Repetition rate	1.6 Hz
Energy and pulse width	No information

Energy density	2.5 to 3.5 J/cm²
Number of pulses, number of treatment sessions, interval between sessions	From 7000 to 8000 pulses per session 3 sessions with an interval of 21 days between sessions.

Author, year, country and title	Storchi IF, Parker S, Bovis F, Benedicenti S, Amaroli A 2018; Italy Outpatient erbium: YAG (2940 nm) laser treatment for snoring: a prospective study on 40 patients. Med Sci Lasers 33:399–406
Study design	Cohort study, without control group
Study N, use of control group	40
Diagnosis	Primary snoring and different degrees of OSA on examination by an otolaryngologist and performing a Muller maneuver to rule out pharyngeal obstruction.
Age and gender	29 men and 11 women, mean age 53 years
Inclusion criteria	No information
Exclusion criteria	Pediatric patients, pregnancy and central apneas, laryngeal obstruction.
Irradiated region	Soft palate and uvula and tonsil regions, including the anterior and posterior pillars and the base of the tongue behind the circumvallate papillae as far as the patient anatomy and compliance would allow.
Outcome measures	Mallampati and Friedman classification, Epworth scale, AHI, VAS pain scale, statistical analysis by Wilcoxon test and $p < 0.05$.
Results	Mallampati and Friedman scale scores decreased significantly ($p = 0.001$) Snoring severity improved significantly after the procedure ($p < 0.0001$) which allowed four couples who slept in separate beds to sleep together again while daytime sleepiness, assessed with the ESS score, was reduced from 4 to a median value of 2 ($p < 0.0001$). Sleep quality showed a significant increase from an initial median value of 5 to a median value of 10 ($p < 0.0001$), and also, the dream intensity perceived by patients increased significantly ($p < 0.0001$). Dry mouth upon waking significantly decreased after laser treatment ($p < 0.0001$), as well as difficulty waking up in the morning ($p < 0.001$) and waking up during sleep because of snoring ($p < 0.0001$).). Notably, in the four subjects with an extravelal tonsil > 50%, the treatment did not appear to be effective. Of the 22 patients with OSAS, only 11 patients agreed to test their sleep using polysomnography after laser treatment. In those patients who agreed to undergo

	polysomnography after treatment, the AHI measurements before and after treatment showed no significant difference (p = 0.08). Patients who did not show improvement in the AHI on polysomnography nevertheless noted subjective improvement and were instructed to proceed with additional treatments for the treatment of OSAS.
Follow-up time	20 months (by telephone interview)
Complications	Very mild sore throat in 1 of 40 patients
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) Pulsed emission mode
Operation mode	LP mode, without contact with at least 7 to 8 laser scans of all regions, with overlapping of the entire mucosa.
Average power	No information
Point diameter	Quote only PS04 handpiece and collimated beam
Source-tissue distance	Quote contactless mode
Repetition rate	10 Hz
Energy and pulse width	No information
Energy density	In the range of 1.6 J/cm^2
Number of pulses, number of treatment sessions, interval between sessions	The number of treatment pulses administered per region and per patient depended on the severity of the Muller test score, the person anatomy, the presence or absence of apneas, and the severity of symptoms and ranged from a low of 11,086 to a high of 25,689 shots. Three sessions were performed on day 0, day 15 and day 45.

Author, year, country and title	Shiffman HS., Matjaz Lukac M. 2018, Slovenia NightLase®: Minimally Invasive Laser-Assisted Uvulopalatoplasty. Journal of the Laser and Health Academy ISSN 1855-9913 Vol. 2018, No.1; www.laserandhealth.com
Study design	Case report, retrospective
Study N, use of control group	Does not quote, but shows photos of 4 patients
Diagnosis	No information
Age and gender	No information
Inclusion criteria	No information
Exclusion criteria	No information
Irradiated region	The soft palate and uvula are treated in horizontal lines with 5 full passes per line in a slow sweeping motion.
Outcome measures	Mallampati classification; snorelab app for snoring; CBCT for UA volume and area of greatest constriction.
Results	Mallampati rating reduced from 4 to 2; snoring time was reduced from 68% to 38%, and the snoring score was reduced from 85 to 51. Airway volume increased by 14% and minimum cross-sectional area doubled from 76 mm^2 to 156 mm^2.
Follow-up time	No information

Complications	No needles or anesthesia are required, other than the occasional use of topical anesthesia. Post-treatment pain is negligible
Laser type, wavelength, emission mode	Nd:YAG ($\lambda = 1064$ nm) and Er:YAG ($\lambda = 2940$ nm); (LightWalker®, Fotona doo, Slovenia) pulsed emission mode
Operation mode	To Er:YAG: Smooth mode
Average power	Nd:YAG:10 W; Er:YAG: 2 W
Point diameter	Quote R30 Nd:YAG handpiece with stitch size of 8 mm on fabric); for Er:YAG handpiece R16
Source-tissue distance	No information
Repetition rate	Nd:YAG: 8 Hz; Er:YAG: 1.5 Hz
Energy and pulse width	Nd:YAG: 25 ms
Energy density	Er:YAG: 3.5 J/cm^2
Number of pulses, number of treatment sessions, interval between sessions	The complete treatment consists of three 20-minute sessions over a period of 45 to 60 days.

Author, year, country and title	Frelich, H.; Scierski, M.; Markow, M.; Frelich, J.; Frelich, H.; Maciej, M. 2019; Poland. Minimally Invasive Rebio Laser Treatment for Selected Snorers (Lasers in Medical Science)
Study design	Cohort study, without control group
Study N, use of control group	24 patients (18 men and 6 women)
Diagnosis	snoring
Age and gender	> 18 years old, both sexes (18 men and 6 women)
Inclusion criteria	> 18 years old, both sexes, BMI < 35, absence of systemic diseases, informed consent, previous consultation with an otolaryngologist with Muller maneuver to check for upper airway collapse.
Exclusion criteria	UA obstruction from causes other than soft palate hypertrophy
Irradiated region	Oropharynx: palatoglossal and palatopharyngeal arches, soft palate, uvula, tonsils and base of tongue
Outcome measures	Household polysomnography (AHI, O$_2$ saturation, desaturation index, ODI, snoring time, snoring time rate) and questionnaires at baseline and 3 months after treatment, statistical analysis by Wilcoxon test comparing before and after treatment ($\alpha = 0.05$).
Results	All variables showed improvement. Statistical difference was observed in the Hypopnea Index (p = 0.034). The sleep quality, quality of life questionnaires of patients and companions were statistically different.
Follow-up time	3 months
Complications	No information
Laser type, wavelength, emission mode	Er:YAG laser 2940 nm; pulsed emission mode
Operation mode	Far pulse, PS04, 7mm spot; with 7 to 8 laser scans and

	50% overlap.
Average power	6.9 W to 7.75W
Point diameter	7mm
Source-tissue distance	No information
Repetition rate	10 Hz
Energy and pulse width	No information
Energy density	1.8 to 2 J/cm²
Number of pulses, number of treatment sessions, interval between sessions	3 treatment sessions; 2 weeks interval between calls, 15000 pulses per session.

Author, year, country and title	Monteiro L, Macedo A, Corte-Real L, Salazar F, Pacheco JJ. 2020; Portugal Treatment of snoring disorder with a non-ablative Er:YAG laser dual mode protocol. An interventional study. J Clin Exp Dent. 2020 Jun 1;12(6): e561-e567
Study design	Cohort study, prospective study
Study N, use of control group	30
Diagnosis	Snoring and OSA (without reporting severity)
Age and gender	Age between 18 and 65 years; 22 men and 8 women; average age 42 years
Inclusion criteria	Patients diagnosed with snoring disorder, both sexes, aged 18 years or older, seen on polysomnography.
Exclusion criteria	Patients under 18 years of age, pregnant women, patients with heart problems, diagnosed with central apnea or laryngeal obstruction, patients using photosensitive drugs, patients with alcohol misuse, patients already treated surgically or with other ongoing treatments (including braces – MAD), patients who were unable to perform the 3 follow-up sessions or consultations, and patients who did not cooperate.
Irradiated region	Oropharynx (soft palate, anterior and posterior pillars uvula and remainder of oropharynx).
Outcome measures	Mallampati classification; from Friedman; questionnaires, snoring intensity by snorelab application; statistical analysis by Wilcoxon matched pair test and McNemar test, with $p < 0.05$
Results	ESS scale difference $p = 0.002$; snoring VAS $p < 0.001$; snorelab $p < 0.001$; Mallampati scale $p = 0.001$; Friedman scale $p < 0.001$
Follow-up time	1 month for clinical assessment and other outcome measures and 6 months for questionnaires and telephone interview.
Complications	No patients reported adverse effects at one-month follow-up.
Laser type, wavelength, emission mode	Er:YAG (= 2940 nm) pulsed emission mode
Operation mode	Long pulse mode in brushing technique with 6 laser

	scans in well-defined overlaps and smooth mode performing 4-6 shots with 6 passes, with overlap around 50%
Average power	No information
Point diameter	PS04 handpiece with 7 mm spot size.
Source-tissue distance	Quote only without contact
Repetition rate	In long pulse mode: 12 Hz; in smooth mode: 2 Hz
Energy and pulse width	No information; it says long pulse mode
Energy density	In long pulse mode: 2 J/cm^2 and in smooth mode: 8 to 10 J/cm^2
Number of pulses, number of treatment sessions, interval between sessions	Total pulses between 10,000 and 12,000 pulses per session; Three sessions, with an interval of 14 days between sessions.
Author, year, country and title	Neruntarat C, Khuancharee K, Shoowit P. 2020; Tailândia Er:YAG laser for snoring: a systematic review and meta-analysis. Lasers Med Sci. 2020 Aug;35(6):1231-1238.
Study design	Systematic review and meta-analysis
Study N, use of control group	7 studies included; 247 participants treated with 2 to 3 treatment sessions with Er:YAG laser, long pulse mode, 10 Hz, fluence 1.6 J/cm^2).
Diagnosis	Er:YAG laser treatment will provide significant improvement in both subjective and objective outcome measures.
Age and gender	Population studies: over 18 years old with snoring, sleep apnea, sleep apnea and sleep disorder; interventions: treatment with Er:YAG; comparison: standard care as a control group or pre- and post-treatment; Results: snoring score, patient satisfaction, snoring reduction, Mallampati classification, apnea-hypopnea index (AHI) and respiratory disturbance index (RDI), side effects and other outcomes such as Friedman tongue position, Muller and Epworth Sleepiness Scale; and design type: experimental studies that were a randomized controlled trial (RCT) or controlled clinical trial (CCT) or prospective/retrospective study that were published in English.
Inclusion criteria	Qualitative and protocol studies
Exclusion criteria	The initial electronic search resulted in 1427 titles from MEDLINE-PubMed, CENTRAL, Scopus database, Cochrane Library and Web of Science and 121 additional records identified through other sources. Of these studies, 1,475 articles were selected using Endnote to remove duplicates and a total of 73 articles were considered for possible inclusion. Subsequently, 31 articles were removed based on their title and abstract. In all, 42 full-text articles were selected. Of these, 35 articles were excluded due to studies lacking

	sufficient data or being reviewed. Finally, seven studies were included in the review.
Irradiated region	Seven studies with 247 participants. All studies were level 4 evidence (case series). There were no multicenter studies, randomized controlled trials, systematic reviews or meta-analyses. All studies had adequate exposure measures. However, all studies had inadequate selection of participants, inadequate confirmation and consideration of confounders, and inadequate blinding of outcome assessments; one of the seven studies had inadequate treatment of incomplete outcome data, and five studies presented results selectively. The average age of participants was 44.8 years and most participants were male.
Outcome measures	Meta-analysis was performed with RevMan and the Cochran Q and I statistical test, used to verify heterogeneity, the general effect was analyzed by the Z test. Pooled meta-analysis results from two studies reported change in pre- and post-treatment snoring VAS scores with statistically significant reduced mean difference and durability at follow-up of 28 to 36 months and 14 to 24 months (MD – 95% CI – 6.89). Pooled meta-analysis results from four studies reported that treatment and patient satisfaction outcomes were consistently better after laser treatment. The combined patient satisfaction rate was 80.00%. Three studies reported Mallampati Classification in patients before and after laser treatment. There was improvement in the airway after treatment (p = 0.001). It increased subjective sleep quality, but did not reduce AHI or RDI.
Results	The level of evidence of the included articles was different and the results were at high risk of bias. Snoring criteria and other parameters were inconsistent. The selection of symptoms suitable for treatment was not the same with the lack of a control group. The sample size in two studies was small with 10 to 11 cases with the largest size being 75 cases. There is some heterogeneity. The studies were showing subjective data. Objective measurements of snoring are necessary to accurately document effectiveness. A median follow-up period in this study was 3 to 36 months. Long-term follow-up is necessary to verify the success of laser treatment. Selection of patients with appropriate tests and exclusion criteria is essential to identify the necessary therapy. However, Er:YAG laser treatment reduces snoring for at least a certain period. Lasting effects of more than a year allow for high overall satisfaction. The studies included in this systematic review and meta-analysis show a statistically significant decrease in snoring after

	treatment.
	The study showed that patients responded positively to laser treatment, which was effective in reducing snoring, improving sleep quality, but not reducing AHI or RDI. In the future, there should still be more randomized controlled trials with multicenter cooperation and long-term follow-up to assess the efficacy of this laser in snoring.
Follow-up time	variable
Complications	Side effects included mild sore throat in 2.5 to 3.5%, which resolved spontaneously without analgesic treatment, temporarily altered palatal sensation in 2 of 33 cases, and brief sensation of dry throat or foreign body in 7 of 33 cases. Serious adverse effects were not found.
Laser type, wavelength, emission mode	Er:YAG laser, pulsed emission mode
Operation mode	long pulse mode
Average power	No information
Point diameter	No information
Source-tissue distance	No information
Repetition rate	10 Hz
Energy and pulse width	No information
Energy density	fluence 1.6 J/cm^2
Number of pulses, number of treatment sessions, interval between sessions	3 treatment sessions

Author, year, country and title	Shiffman HS, Khorsandi J, Cauwels NM. 2021, EUA Minimally Invasive Combined Nd:YAG and Er:YAG Laser-Assisted Uvulopalatoplasty for Treatment of Obstructive Sleep Apnea. Photobiomodul Photomed Laser Surg. 2021 Aug;39(8):550-557
Study design	Case series, retrospective study
Study N, use of control group	27, no control group
Diagnosis	OSA (AHI > 5)
Age and gender	Age between 25 and 78 years; 20 men and 9 women
Inclusion criteria	Age over 18 years, AHI > 5
Exclusion criteria	Patients under 18 years of age, pregnant women, patients diagnosed with central apnea or laryngeal obstruction, patients using photosensitive drugs, patients with alcohol abuse, patients already treated surgically or undergoing other treatments (including oral appliances), patients who could not perform the three follow-up sessions or consultations and non-cooperative patients. Two male patients were excluded from further analysis (AHI < 5).
Irradiated region	Nd:YAG: Soft palate and uvula;

	Er:YAG: palatopharyngeal and palatoglossal arches, soft palate and uvula
Outcome measures	AHI measurements, oropharyngeal photographs; statistical analysis with paired t test.
Results	Decrease in AHI for all patients with different OSA severities tested in this study was achieved, with a mean improvement of 66.3% (32-100%).
Follow-up time	Only up to 1 month after the last treatment session
Complications	Occasional, mild, temporary sore or dry throat sensation in the postoperative period.
Laser type, wavelength, emission mode	Nd:YAG (= 1064 nm) e Er:YAG (= 2940 nm) pulsed emission mode
Operation mode	For Nd:YAG: it only mentions that the laser light was delivered in horizontal lines in forward and backward motions. Five complete tickets were delivered for each line. For Er:YAG: Smooth mode. Four to six shots per point before moving to the adjacent point with minimal overlap to gradually increase mucosal temperature without causing any ablation. Multiple passes (6) following the same pattern were performed on the entire right side of the oropharynx and mirrored on the left side. Occasional application of topical anesthesia was used.
Average power	Nd:YAG: 10 W; Er:YAG: 4 to 5.15 W
Point diameter	Nd:YAG: R30-A handpiece with 2 mm dot size used blurred to 8 mm on tissue. Er:YAG handpiece Er:YAG PS04 with 7 mm diameter spot size.
Source-tissue distance	For Nd:YAG: does not quote; for Er:YAG quotes contactless
Repetition rate	To Nd:YAG: 8 Hz; to Er:YAG: 1.5 Hz
Energy and pulse width	To Nd: YAG: 25ms; to Er: YAG: it doesn't say.
Energy density	Nd:YAG: 40 J/cm²; Er:YAG: 7 to 9 J/cm²
Number of pulses, number of treatment sessions, interval between sessions	For Nd:YAG: 900–1200 pulses as the endpoint, according to the patient pharyngeal anatomy. For Er:YAG: 7000 to 9000 pulses. Three 20-minute sessions were performed 3 to 4 weeks apart between sessions.

Author, year, country and title	Valerie A. Picavet; Marc Dellian; Eckard Gehrking; Alexander Sauter; Katrin Hasselbacher 2022/jun; Germany
Study design	Controlled and randomized clinical trial
Study N, use of control group	N = 40; use of control group
Diagnosis	Primary snoring and mild OSA (AHI < 15), by any type of polysomnography
Age and gender	> 18 years; experiment group: mean age: 43.3 years; 7 women and 13 men; control group: mean age: 44.5

	years; 5 women and 15 men.
Inclusion criteria	> 18 years, primary snoring and mild OSA; BMI < 30, no EDS (ESS < 10), with understanding of SBD and request for treatment.
Exclusion criteria	Nasal obstruction and tonsillar hypertrophy
Irradiated region	Oropharynx: posterior part of hard palate, soft palate, anterior and posterior pillars, tonsils, uvula and base of tongue.
Outcome measures	Patient Snoring Outcome Questionnaire (SOS: 8 items related to intensity, duration, frequency, and impact on SBD symptoms – specifically snoring and roommate snoring (SBPS), with scores ranging from 0 (worst) to 100 (better); VAS scale (0 = no snoring and 10 = severe snoring/sleeping apart) for roommate; immediately after consultations and on days 1 and 3 after each consultation, patients responded to the VAS pain scale (0 = no pain and 10 = worst pain); dry throat, altered taste, or other different sensation. By sum of classification of two samples, statistical U test, p-value < 0.05 considered statistically significant, by ASA 9.4 (SAS Institute).
Results	At 3-month follow-up: SOS and SBP questionnaires without change in the control group; in the experimental group: difference in the 2 questionnaires and VAS scale of snoring for roommate with p < 0.001.
Follow-up time	3 months.
Complications	VAS scale for pain in the immediate postoperative period = 3.3; 1 day after = 0.3 and 3 days after = 0, with transient and mild effects including throat dryness.
Laser type, wavelength, emission mode	Er:YAG; 2940 nm, smooth mode; Fotona Sp Dynamic; PS03X (7mm spot)
Operation mode	Smooth mode; 4 to 6 shots per point, no overlap
Average power	No information
Point diameter	7 mm
Source-tissue distance	It just says that the tip allows the delivery of energy without changing the size of the point and without blurring
Repetition rate	2.2 Hz
Energy and pulse width	No information
Energy density	8.5 – 9 J/cm²;
Number of pulses, number of treatment sessions, interval between sessions	2011 to 2297 pulses per session; 3 visits (day 0; day 14 to 21; day 42).

A literature review on clinical effects of laser use in SBD management showed that publications are scarce and little explored. The effects of laser treatment were explored from the point of view of histology in palatine mucosa of rats, in 2016 by Unver T. and his

collaborators. Tissue retraction without evidence of exacerbated inflammation, tissue carbonization or necrosis was the main finding. Other authors have published their findings of airway volume expansion, clinical improvement reported by patients, but without observance of correspondence in the improvement of objective parameters of SBD. Shiffman et al., in a study published in 2021, observed a decrease in AHI of all OSA patients, with an average improvement of 66.3%, when associating Nd:YAG laser with Er:YAG laser. Level of evidence in publications, due to the design adopted in studies, is weak, which makes it difficult to establish whether or not to recommend the treatment. In addition, irradiation parameters were not clear in most publications, despite the therapeutic option being promising. [64-77]

The systematic review and meta-analysis, despite limitations, showed a statistically significant reduction in snoring and revealed an enlargement of upper airway dimension after treatment. However, changes in apnea-hypopnea index (AHI) were not significantly important in most studies. The clinical trial used subjective measurement as a parameter for analyzing its results. Other parameters need to be analyzed. Performance of controlled, randomized clinical trials using objective measures for results evaluation, long-term follow-up and adequate design to reduce possible bias, would bring greater evidence regarding the therapeutic benefit proposed for SBD laser treatment. [64-77]

This study is necessary to elucidate the new therapeutic proposition for SBD, in Brazilian population and in the world.

4.2 Radiation technology in health sciences

Radiation consists of electromagnetic waves or particles that propagate with high speed and, therefore, energy of variable value. It can produce varied effects on matter, resulting from its interaction with it, being generated by natural sources and/or built by man. [78]

Electromagnetic radiation can be defined as the set of electric and magnetic waves whose speed in vacuum is given by $c = 3 \times 10^8$ m/s. The various radiation forms, characterized by their wavelength, make up the electromagnetic spectrum. [78]

Figure 8 – Electromagnetic spectrum
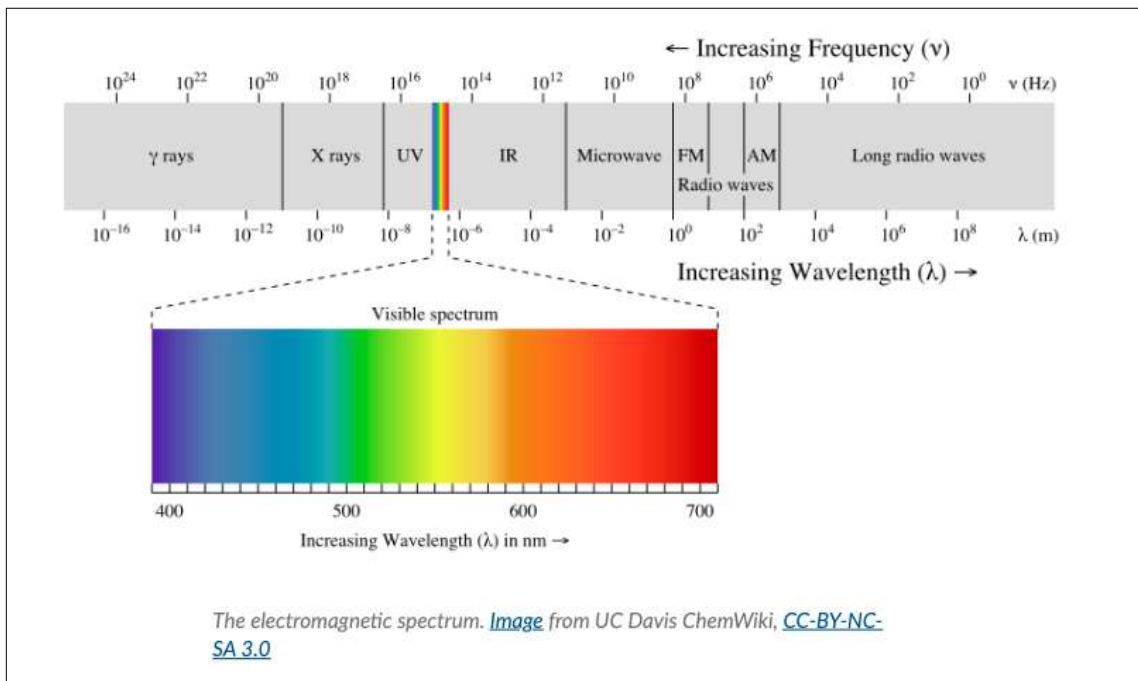
Source: Electromagnetic Spectrum – available at UC Davis ChemWiki, CC-BY-NC-SA 3.0.

Radiation is considered ionizing when the radiation beam has enough energy to remove electrons and break chemical bonds, thereby creating ions. It is spontaneously emitted from the nucleus of atoms. X-rays, gamma rays, positrons, alpha particles, beta particles and some ultraviolet rays are examples of this type of radiation.[79]

Ionization energy for elements found in biological tissues is in a range that varies from 3.5 to 20 electron volts (eV). Non-ionizing radiation is, therefore, the modality of low-frequency, low-energy radiation that propagates as an electromagnetic wave, consisting of an electric field and a magnetic field, which may come from natural and unnatural sources. It originates from electrons movement (electrical charges).[80]

Figure 9 – Ionizing radiation x non-ionizing radiation

58
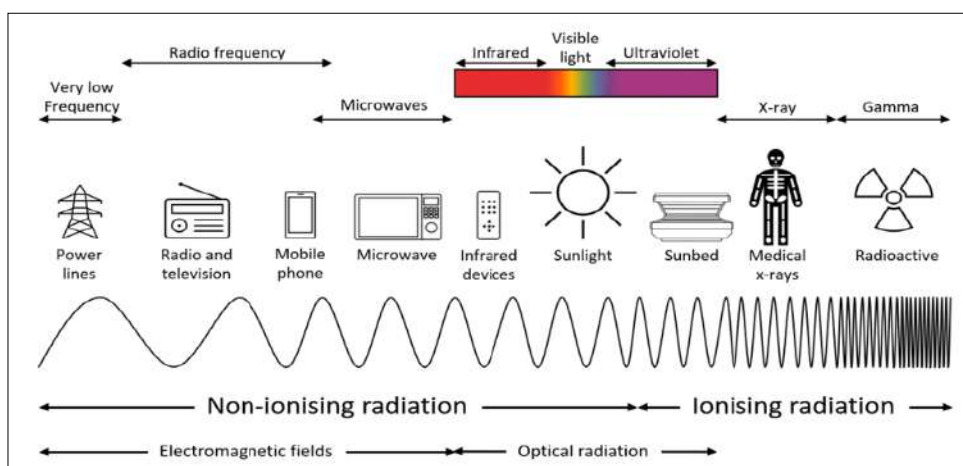
Light, radiant energy, plays a fundamental role for living beings, in general, participating in several daily biological processes, such as photosynthesis and fixation of vitamins in human beings. The use of sunlight for some pathologies treatment, known as heliotherapy, already had an established application in Egypt and ancient Greece. [81,83]

Visible light can be defined as a source of electromagnetic energy that propagates in waves, at a constant speed, with wavelength in vacuum between 400 nm and 700 nm, within the electromagnetic spectrum. Photon, a massless particle, is the basic unit of this radiant energy. Its propagation is wavelike, resulting from the combination of electric and magnetic fields that vary in time and space. Electron-volt (eV) is the usual unit of photon energy measurement. It can be converted into Joule (J) or calorie (cal).[81,83]

4.2.1 Laser

Laser is an acronym for Light Amplification by Stimulated Emission of Radiation. Laser is light, therefore, electromagnetic radiation composed of photons, which propagates in waves.[81,83]

In this work, we used non-ionizing electromagnetic radiation, since Nd:YAG laser (yttrium-aluminum-garnet matrix doped with neodymium), with 1064 nm wavelength, emits photons with energy of 1.16 eV and Er:YAG laser (yttrium-aluminum-garnet matrix doped with erbium), with a wavelength of 2940 nm, emits photons with 0.422 eV energy.[83,86]

In 1917, physical principles of stimulated emission, on which the laser phenomenon is based, were theoretically described by Albert Einstein. Charles Townes, in 1951, developed a predecessor of laser – the Maser, acronym for "microwave amplification by stimulated

emission of radiation" and in 1958, with the collaboration of Shawlow, the laser was proposed. In 1960 the first equipment – a Ruby laser – came into operation in the United States, developed by Theodore H. Maiman. [83,84]

In 1965, Sinclair and Knoll adapted this radiation to therapeutic practice and in the same year ruby laser was used for the first time in Dentistry by Stern and Sognaes.[83,84]

Thermal effects of the continuous wave lasers at that time would damage the dental pulp. Researchers found clinical use for oral soft tissues through use of medical carbon dioxide (CO_2) and Nd:YAG lasers. In 1990 pulsed Nd:YAG laser, designed for the dental market, was launched. In the 1990s, semiconductor-based diode lasers also appeared. In 1997, for the first time, dental hard tissue was removed using the Er:YAG laser and, in the following year, with the Er,Cr:YSGG laser (Gallium oxide, scandium, and yttrium doped with erbium and chromium). [83.84]

Resolution Nº. 82, of the Federal Council of Dentistry of September 25, 2008, recognized the practice of laser therapy by qualified dental surgeon, having a field of action for diagnosis and treatment of pathologies that encompass maxillomandibular complex, the lower limit being hyoid bone.[63]

4.2.2 Interaction of electromagnetic radiation with biological tissue

To be beneficial in health applications, the use of light sources needs to be very well controlled. Because of its coherence, collimation and monochromaticity properties, laser light is more suitable for a variety of applications.[81,83,85]

4.2.3 Determination of laser-tissue interaction by laser-related factors

- wavelength (determines the depth of optical penetration into the tissue);
- energy density of light beam (whose value is a necessary condition for occurrence of a certain effect and its extent). It is the amount of energy per area unit transferred to matter, generally measured in J/cm^2;
- average laser power (important for power and energy density calculations). For continuous operation mode, laser power remains constant and is equal to average power. When laser regime is pulsed, power varies between a maximum value (peak power) and zero, but average power is still the parameter used in calculation;

- power density of light beam, also called intensity. It is the beam power per unit area, usually measured in W/cm^2. Expresses relationship between energy density and pulse duration;

- temporal characteristics of the energy beam (continuous and pulsed emission);

- pulse width is the time during which laser output power remains on continuously in a period of time. Pulse duration governs spatial confinement of heat (determines the effect on biological tissue, in particular, thermal and non-thermal effects can be distinguished);

- pulse repetition frequency or rate (it is the number of pulses per second), measured in Hertz (Hz);

- diameter of light beam;

- presence or absence of external cooling;

- Average Power: expressed in Watt (W) = E (J) x f (Hz)

- Peak Power: is measured in Watt (W)

- Energy (J) = (P.t) [81,83,85,86]

4.2.4 Determination of laser-tissue interaction by tissue-related factors

Added to the properties of light, there are biological factors influencing laser-tissue interaction, such as the optical (reflection, absorption and scattering coefficient), physical (skin color, distribution of adipose tissue and systemic condition) of each tissue, in addition to mechanical and physiological processes resulting from the interaction, such as heat conduction and dissipation, inflammatory response, vascularization and repair mechanisms. [81,83,85,86]

Interaction between laser and living tissue can occur in five ways:

- By reflection, when the incident light beam is reflected on tissue surface, without penetration or interaction, returning to incident radiation source. When the surface is smooth (with small irregularities compared to wavelength of incident radiation), specular reflection occurs. When surface roughness is equal to or greater than the wavelength of incident radiation, diffuse reflection occurs (a common phenomenon for biological tissues);

- By refraction, when a reflective surface separates two media of different refractive indices; and this phenomenon occurs as consequence of a change in the incident beam velocity;

- By transmission, when a beam part is transmitted through the tissue, without causing an effect;

- By absorption, when an electromagnetic wave does not return from the incident surface and does not propagate in the environment. Energy transfer occurs and part of radiation is absorbed and converted into heat or vibration of tissue molecules by one or more chromophores. Environment ability to absorb electromagnetic radiation depends mainly on the electronic constitution of its atoms and molecules, wavelength of radiation, absorbing layer thickness and internal parameters, such as temperature and concentration of absorbing agents. Two laws are often applied to describe both effects of thickness. Lambert law, effect of concentration and Beer law, on absorption. In biological tissues, absorption is mainly caused by water molecules and macromolecules, such as proteins and pigments;

- By scattering, when a remnant of light penetrated the tissue and spread through it, being able to be absorbed in distant regions from that incidence.

Laser-tissues interaction occurs when there is optical affinity between them. This affinity is based on absorption and scattering. The lower the affinity, the greater the reflection or transmission of light. [81,83,85,86]

Figure 10 – Interaction between laser radiation and biological tissues.
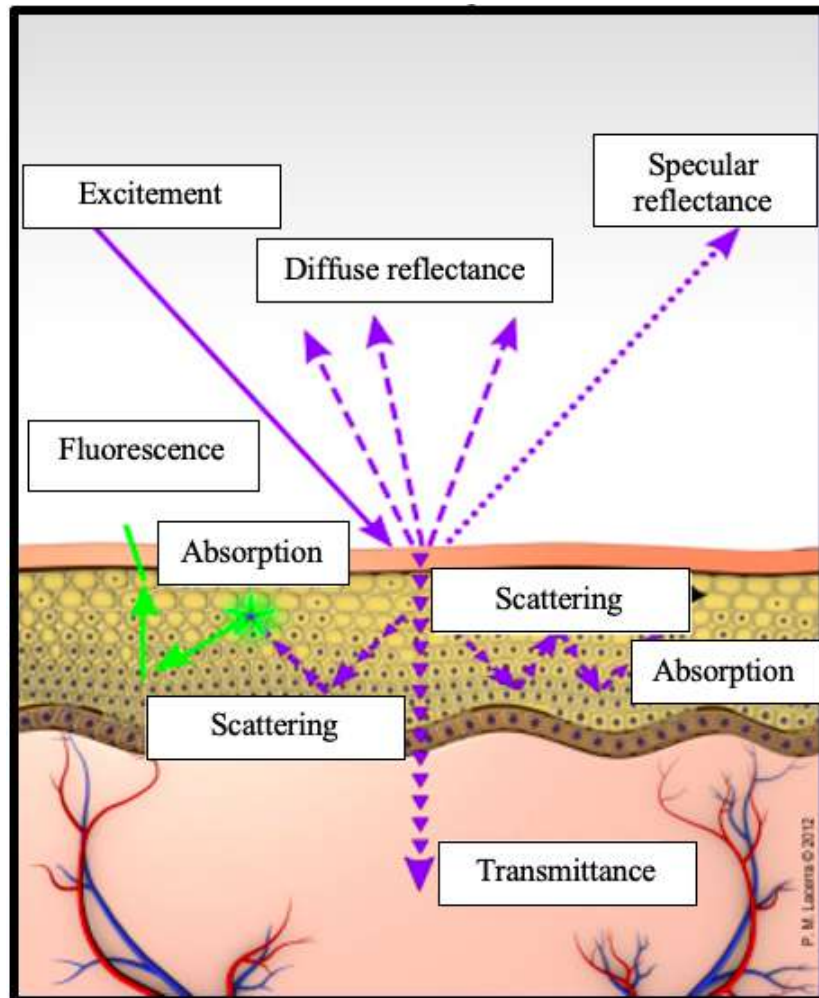
Source: Bachmann L, Zezell DM. Laser Physics and Laser Tissue Interaction. In: Caprioli C, Vitale MC organizadores. Lasers in Dentistry – Practical textbook. Italy: Edizioni Martina; 2009. p. 01-14.

Chromophores are tissue components that absorb light energy. Main chromophores of biological tissues are hemoglobin, melanin, proteins and water. A complex biological system is made up of numerous cells and fluids, with different optical absorption characteristics. It is therefore necessary to analyze the optical absorption spectrum of each tissue to then select the wavelength most strongly absorbed by that.[81,83]

When chromophores (charged and elastically confined particles) are exposed to electromagnetic waves, their movements become according to the incident electric field. If wave frequency is equal to natural particle free vibration frequency, resonance occurs, accompanied by a considerable amount of absorption.[81,83]

Scattering occurs when wave frequency does not correspond to natural particle frequency. Resulting oscillation is determined by the forced vibration, with its phase different

from that of the incident wave, causing a decrease in speed of photons penetration in a dense environment. Therefore, scattering can be considered as the basic origin of scattering. Depending on way in which incident photon energy is converted, there is either elastic or inelastic scattering.[81,83]

In elastic scattering, incident and scattered photons have the same energy. A special case of elastic scattering is Rayleigh scattering (scattering is inversely proportional to the fourth power of the wavelength). Its restriction is that scattering particles be smaller than incident radiation wavelengths. When scattering particles have an extension comparable to incident wavelength, Rayleigh Scattering is not applicable and another type of phenomenon is defined: Mie Scattering, which shows weak dependence on wavelength, when compared to Rayleigh. Mie scattering prefers the direction of incident wave.[81,83]

In biological tissues, photons are preferably scattered in the same direction as the incident beam. This phenomenon cannot be explained by Rayleigh scattering. Furthermore, wavelength dependence is stronger than what Mie Scattering predicts. Thus, neither Rayleigh nor Mie fully describe tissue scattering. Therefore, it is convenient to define the probability of a photon being scattered by an angle θ. If probability does not depend on θ, the scattering is said to be isotropic. Otherwise, scattering is called anisotropic.[81,83]

In turbid environments, such as biological tissues, anisotropy and scattering coefficients are related by the same parameter, called reduced scattering coefficient. For most biological tissues, anisotropy coefficient has values between 0.7 and 0.99 and scattering angles are between 8° and 45°.[81,83]

Therefore, laser-tissue interaction occurs in several ways. But for a biological response to occur through interaction, it is necessary that radiation be absorbed and produce a change in this environment. Understanding tissue constitution of the region to be treated, healing process and its phases, in addition to optical principles of light, allow establishment of adequate parameters to achieve the expected effect. [81,83]

4.2.5 Photon energy absorption and establishment of a biological response

Photon interaction with living tissue takes place at molecular level, through its absorption (energy) and subsequent de-excitation.[87]

Tissue is made up of different types of molecules (water, proteins, fats) and each of them absorbs different wavelengths and behaves in a unique way. Therefore, wavelength choice specifically determines where and the way interaction takes place.[87]

Energy absorbed from photons by molecules can occur in form of kinetic energy, electronic energy and nuclear energy. When an electron absorbs the photon energy, it moves to a higher energy level, in an excited state (provided that photon and electron have a resonant energy level). From the excited state, the electron tries to release the accumulated energy, decaying to the lowest energy level. This release of energy can happen in form of a photon emission or molecular vibration, for example. When electrons in a molecule return to their ground state, the molecule is said to be in a singlet state.[87]

Molecules are composed of protons (positive charge) and electrons (negative charge) which, when added together, result in overall residual charge, referred to as an electric dipole. When a molecule encounters a photon alternating electric field (oscillates, changing polarity, at a certain frequency), it will move as the electric dipole aligns itself. If molecule is structured so that photon frequency matches its frequency, they are said to be resonant, and photon energy can be transferred to molecule (absorption), but it will only occur if there is an energy level to which the molecule can move with that amount of extra energy.[87]

The energy acquired by photon absorption will begin to be redistributed within the molecule until equilibrium occurs. However, a jump to a lower energy state can also occur, with emission of a photon. In fluorescence there is a rapid transition from one state to another. Phosphorescence occurs after intramolecular redistribution, and so radiation is of lower energy and occurs over a longer time scale.[87]

When light absorption gives rise to electronic transition, the more energetic electron will orbit the nuclei at a greater distance. As attractive nuclear force drops rapidly with distance, the electron will be less strongly bound and will be able to form a chemical bond with another molecule more easily. This is the basis of photochemical reaction.[87]

As an excited molecule undergoes intramolecular redistribution, it may collide with another molecule. Part of vibrational energy in the excited molecule will be transferred to the colliding molecule as kinetic energy. Molecular kinetic energy is what appears on a macroscopic level as an increase in temperature, leading to photothermal effects.[87]

Figure 11 – Three of the ways in which the excited state can return to the ground state: thermalization (by collisional and vibrational relaxation), fluorescence (short-lived photon emission) and phosphorescence (long-duration photon emission).
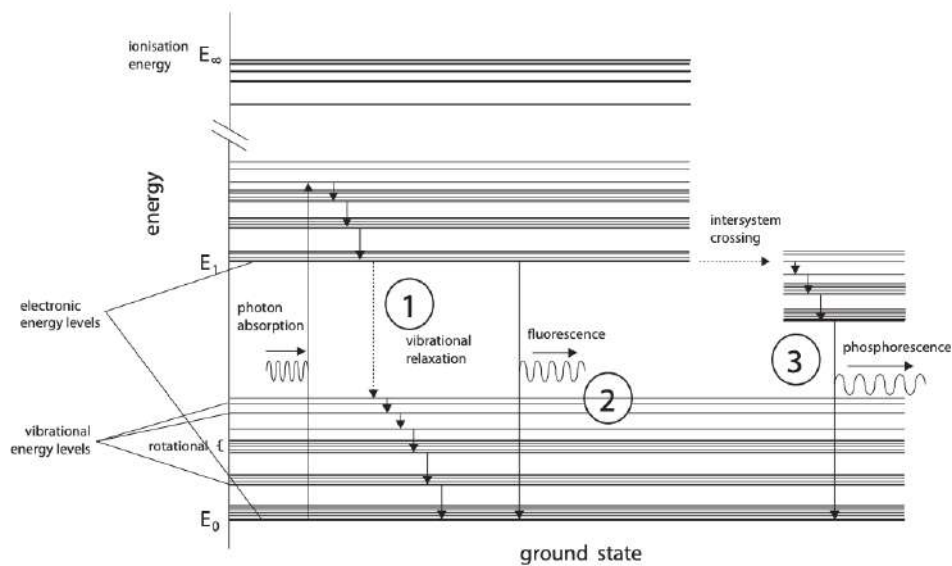
Source: Cox B. Introduction to laser-tissue interactions. 2010. p. 5-11, 22-50. Disponível em: https://www.academia.edu/11072914/Laser_tissue_Interactions

There are different mechanisms by which laser light can interact with tissue. For purposes of this dissertation, the most common interaction mechanisms for health applications will be mentioned and our attention focus will be on photothermal reactions.[87]

a) Photochemical reactions: when energy of laser light (photon) is absorbed by a specific chromophore for that wavelength, capable of inducing biochemical reactions at cellular level, without changes in temperature. They include biostimulation, photodynamic therapy and tissue fluorescence;

b) Photothermal reactions: photons energy absorbed by chromophores is converted into thermal energy through vibrations and molecular collisions, causing thermal effects, by the direct increase in temperature in volume of the irradiated tissue. When this energy is applied long enough, heat conduction will also cause a rise in temperature in surrounding tissues. Thus, thermal effects are produced indirectly in collateral areas to the irradiated target;

c) Photomechanical reactions: occur when the irradiance energy is high enough to form plasma accompanied by high electric fields, dielectric reactions, shock waves and tissue rupture. In photoablation: high energy ultraviolet (UV) photons are absorbed by electrons, elevating them from a lower energy 'bonding' orbital to

a higher energy 'nonbonding' orbital, with virtually immediate molecules dissociation, which leads to rapid expansion of the irradiated volume and ejection of tissue from surface. In photodisruption: mechanical effects can accompany plasma generation, such as bubble formation, cavitation, jets, and shock waves.[87]

The dominant mechanism will depend on:

a) tissue type of molecules and contains (they determine photons energy levels that can be absorbed, as well as the available de-excitation pathways);

b) frequency (or wavelength) of light, that is, energy associated with each individual photon;

c) power per unit area provided by laser;

d) illumination duration and pulse repetition rate for a pulsed laser.

As different interaction mechanisms dominate under different conditions (like photoablation requires UV light, photodisruption requires very short duration pulses) by carefully choosing laser characteristics, interaction can be restricted to a specific mechanism and therefore to a specific tissue effect. Lasers are therefore useful for medical applications because:

• photons energy can be chosen, as each type of laser will emit photons of only one energy (one frequency or wavelength);

• power can be carefully controlled over a wide range of irradiance;

• beam shape can be well controlled (focused, collimated, etc);

• aser pulse duration may vary. [87]

4.2.6 Laser-tissue interaction with photothermal effect production

Thermal effects represent most common form of tissue-laser interaction in clinical practice. Unlike what happens in photochemical reactions, with a specific reaction pathway, which leads to tissue damage, in photothermal reactions, there is no specific pathway. Photons can be absorbed by any biomolecule and generate a thermal effect. Thermal energy is deposited in tissue by absorption of light and its subsequent conversion to heat via collisional

relaxation, causing rise in tissue temperature with subsequent diffusion into surrounding tissue.[81,82,83,86,87,88]

For photons energy to end up as heat in tissue, it is necessary that photons be absorbed by molecules, which are in an excited state. When vibrating, it collides with other molecules, losing energy that is transferred to molecules around it in kinetic energy form. Molecular kinetic energy increase is, on macroscale, the tissue temperature increase. The deposited heat does not stay in the same place for long, it spreads to surrounding tissue. In soft tissue, Fourier conduction law, which says heat will flow in the opposite direction of temperature gradient, from hot to cold. And the relationship established between depth of thermal penetration and time is not linear. In tissue, heat diffuses to about 0.7 μm in 1 μs, to 2.1 μm in 10 μs, to 7 μm in 100 μs, to 21 μm in 1 ms. Time required for heat diffusion or 'thermal relaxation time' is defined as the time required for thermal energy accumulated within the irradiated tissue mass to cool to 37% of its original value. It is directly proportional to the physical size of the target, indicating how quickly an object loses its heat. For processes happening much faster than relaxation time, we can ignore thermal diffusion.[81,82,83,87,88]

Figure 12 – The laser-tissue interaction with the production of direct and indirect photothermal effect.
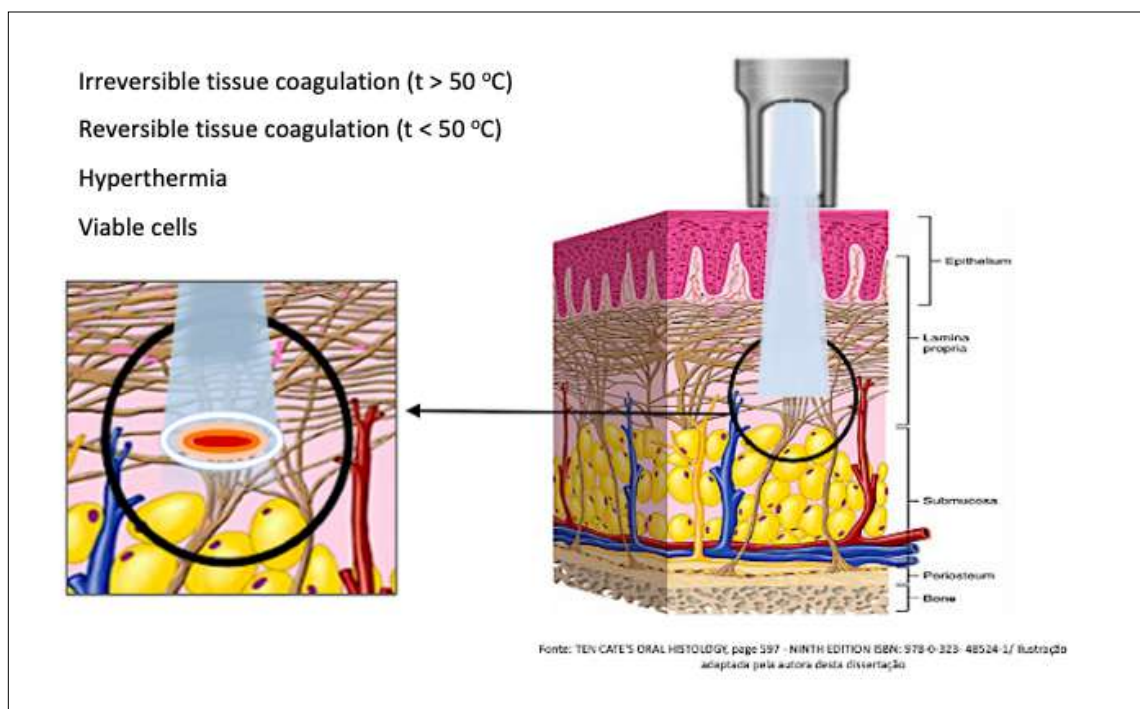
Selective photothermolysis concept refers to a technique by which we choose laser wavelength that is absorbed much more strongly by a chromophore than by surrounding

tissue. Ablation threshold is minimum amount of energy required to generate a clinical ablation effect.[81,82,83,87,88]

To understand how light and tissue thermally interacts, first find out where light energy is being deposited as thermal energy. Second, soft tissue conducts heat, through optical penetration depth and thermal relaxation time concepts. And finally understand what happens to tissue when it reaches a certain temperature. [81,82,83,87,88]

Figure 13 – Laser-tissue interaction: from absorption to thermal effect production.
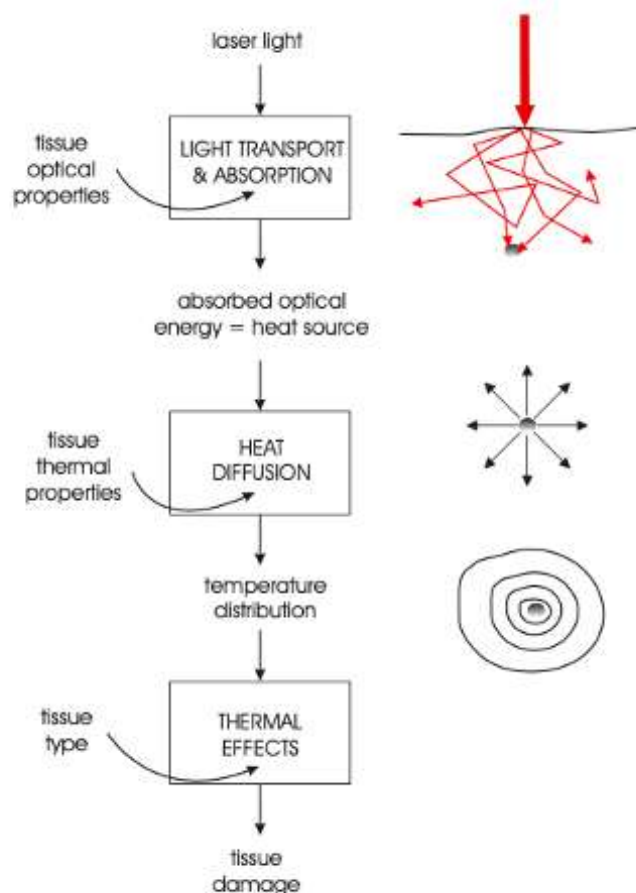
Source: Cox B. Introduction to laser-tissue interactions. 2010. p. 5-11, 22-50. Disponível em: https://www.academia.edu/11072914/Laser_tissue_Interactions

Tissue constitution is, in a simplified way, collagen, water, hemoglobin and other chromophores, such as melanin. Cells will be treated as filled with water, and extracellular matrix (ECM), as a fibrous framework with cells, giving to tissue, rigidity and structure. Collagen, elastin, glycoproteins and proteoglycans are its main components.[81,82,83,87,88]

In ultraviolet ($\lambda < 0.4$ μm) and infrared ($\lambda > 1.5$ μm) electromagnetic spectrum regions, tissue interaction occurs predominantly by absorption and scattering influence is

relatively small. Therefore, light beam does not penetrate deeply into the tissue. Its main chromophores are proteins, water and hydroxyapatite.[83]

In the visible region (between $\lambda = 0.4$ and $\lambda = 0.6$ μm), absorption and scattering occur. Light beam penetration depth is between 0.5 and 2.5 mm. Its main chromophores are oxyhemoglobin, hemoglobin and melanin. [83]

From 0.6 μm to 1.5 μm of electromagnetic spectrum (red and near infrared), scattering predominates over absorption and penetration depth is around 8 to 10 mm. Its main chromophores are oxyhemoglobin, hemoglobin and melanin.[83]

Figure 14 shows the main tissue constituents absorption coefficients.

Figure 14 – Main chromophores of biological tissues
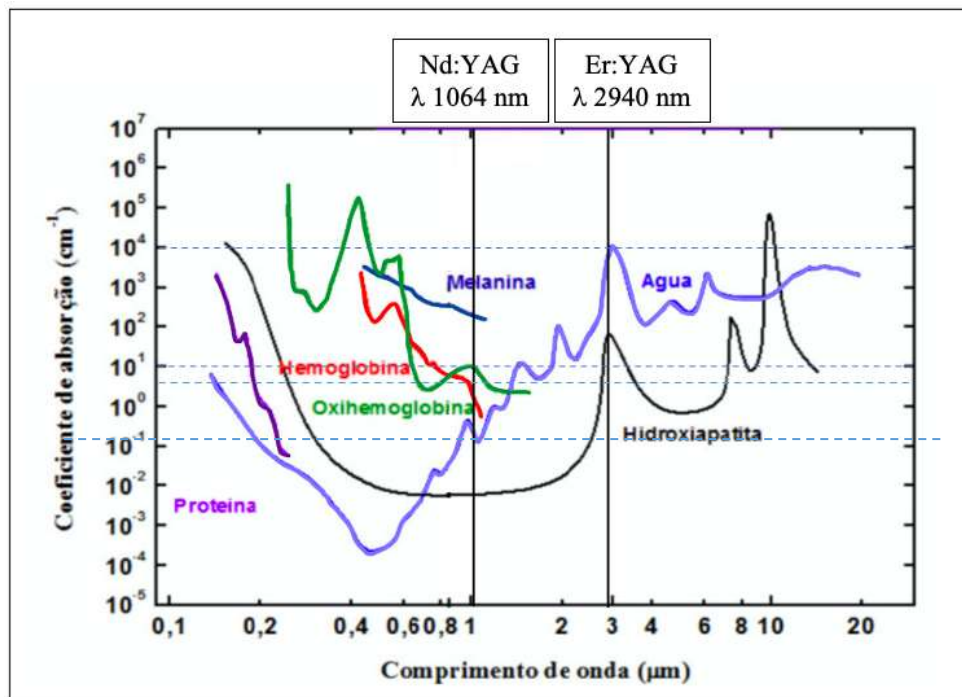
Source: modified from MPLO – Maldonado, P; Ribeiro, MS; Zezell, DM – IPEN.

Temperature effects:

- ∼ 37° C is normal body temperature, and with a few degrees of warming there are few irreversible changes;[81,82,83,87,88]
- At ∼ 41º C, a state of hyperthermia, a series of effects begins. Cellular proteins (membrane or cytoplasmic proteins) begin to undergo conformational (shape) changes because hydrogen bonds are broken by molecule vibrations as temperature

increases. With the conformational change, protein ceases to fulfill its function in the cell. Cells necrose (or apoptosis) rate increases with increasing temperature;[81,82,83,87,88]

- From ~ 45° C, ECM collagen fibers begin to shrink as the collagen tri-helical structure breaks down, initiating a tissue coagulation process. Increasing temperature, volume expansion as water vaporizes can lead to tissue expulsion from the tissue surface. Once all water has evaporated, remaining organic material can char and eventually evaporate.[81,82,83,87,88]

4.2.7 Hyperthermia: damage integral

Tissue injury magnitude, or tissue damaged proportion, dead cells, denatured molecules can be modeled using a 'damage integral' calculation. Arrhenius equation is the usual way of estimating tissue damage proportion after a certain time. It also estimates the time for different tissues to be significantly damaged when kept at constant temperature.[81,82,83,87,88]

Physical process of thermodynamic tissue heating during a thermal pulse is accompanied by chemical denaturing proteins process as a result of cellular exposure to increased temperature. A commonly used metric to estimate tissue damage is the concentration of native (undamaged) tissue ratio before thermal exposure to native tissue concentration at the end of exposure time. Tissue damage over time of thermal exposure is then calculated using the Arrhenius damage integral. According to calculation, tissue damage grows exponentially with elevated temperature and linearly with exposure time. Tissue damage kinetics is commonly characterized by a critical temperature (damage threshold), representing the temperature at which concentration of undamaged tissue is reduced. A single biochemical damage process and a constant temperature square-shaped temperature pulse are assumed during thermal exposure time.[81-83,87,88,90]

Studies on tissue damage dynamics demonstrate that, considering extremely short and long exposure times, cell viability cannot be described by a single biochemical process. Damage threshold temperature measurements at extremely short exposure times (commonly present during Er:YAG laser treatments) exhibit a shift to much higher temperatures than would be expected from a single biochemical process, characterizing dynamic damage over long exposure times. It was recently demonstrated by means of variable heat shock (VHS)

model the dependence of a critical temperature on the time of thermal exposure observed can be described as a combined effect of two limiting factors of Arrhenius equation, defining cell viability at exposures extremely long and short times. In modeling for thermal damage study by Arrhenius integral, only a high and constant temperature is considered during thermal exposure time, based on measurements greater than one second. Therefore, it was assumed a single chemical process accounted for the kinetics of protein denaturation (Arrhenius coefficient, activation energy, and damage rate were fixed regardless of exposure time). However, more recent studies have shown for extremely short exposure times (t_{exp} < 10 milliseconds), the activation energies obtained were significantly lower and damage threshold temperatures were significantly higher than expected by the single-pattern Arrhenius model. This finding was of great importance for non-ablative Er:YAG laser procedures, in which tissue surface is subjected to intense thermal exposure (maximum temperature peaks in extremely short exposure periods) and for long exposure periods at moderate temperatures.[89,90]

4.3 Living tissues

Living tissues are inhomogeneous light-absorbing environments. A part of incident light is reflected (due to Fresnel law: refractive index of tissue is greater than that of air), and other part penetrates the tissue. Part of radiation that penetrates, propagates in tissue, but suffers divergence and attenuation due to scattering and absorption phenomena according to the selected wavelength and irradiated target tissue. [81,82,83,87,88]

Oral cavity can be divided into two parts: external vestibule, delimited by lips and cheek, and oral cavity itself, which is separated from vestibule by alveolar bone and gingiva. Its upper limit is hard and soft palate. As an inferior limit, the floor of mouth and the base of tongue. As posterior limit, the throat isthmus and palatine tonsils.[91,92,93]

Figure 15 – Anatomy of the oral cavity.
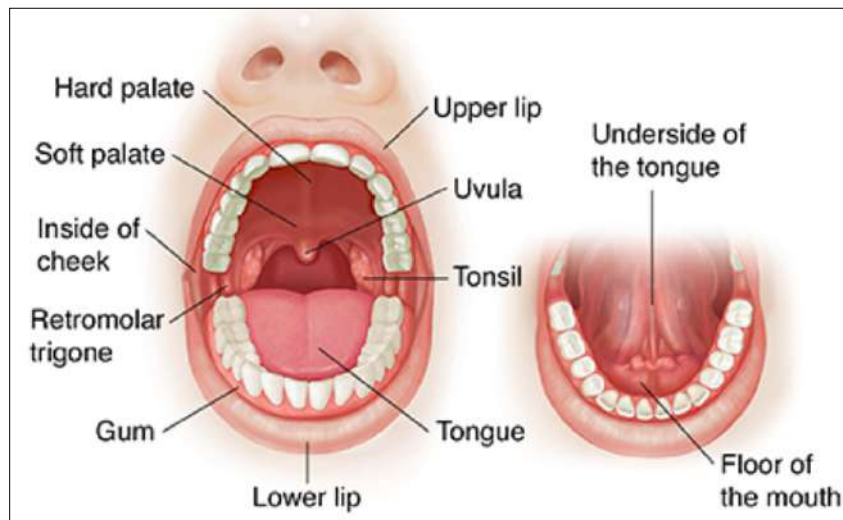
Source: Thibodeau G, Patton K. Anatomy and physiology. 6th ed. St Louis; 2007. Mosby.

Three mucosa types can be identified in the oral cavity, according to their function: masticatory mucosa, specialized mucosa and lining mucosa (this represents 60% of the entire mucosa). Mucous tissue differs from skin in appearance (lips are more stained, due to concentration and dilation of small blood vessels in their connective tissue), thickness of epithelium, degree of keratinization and amount of melanin.[91,92,93]

Main components of oral mucosa are: stratified squamous epithelium, called oral epithelium, and a layer of connective tissue, called lamina propria, separated by the basement membrane. Submucosa is located below lamina propria. It is a layer of loose connective tissue, rich in adipose tissue or glandular epithelial tissue, containing the main blood vessels, minor salivary glands, and nerves. It separates oral mucosa from underlying bone or muscle tissue. Its composition allows flexibility in fixing oral mucosa to other structures. In oral mucosa there are still follicles of lymphoid tissue, associated with crypts formed by invaginations of epithelium towards lamina propria. These areas are heavily infiltrated by lymphocytes and plasma cells.[91,92,93]

Oral epithelium is most superficial portion of oral mucosa. It is a stratified squamous epithelium (with tightly packed cells in distinct layers). Deeper cells are responsible for replacing those flakes off over time. There are two populations of cells: progenitor, in stratum basale, providing new cells, and a maturation one, which continuously differentiate or mature to form the protective surface layer. Cells displaced to the surface after mitotic division can mature in two ways: by keratinization and by non-keratinization. For interest of this dissertation, we will approach the process of maturation by non-keratinization. [91,92,93]

- Lining oral mucosa is not keratinized. It has basal, intermediate and superficial layers;
- Oral epithelial nonkeratinocytes are represented by a variety of cell types, including pigment-producing cells (melanocytes), Langerhans cells, Merkel cells, and inflammatory cells. Together, they represent 10% of oral epithelial cell population;
- Melanocytes responsible for the color of oral mucosa, together with hemoglobin. They produce melanin and are located in basal layer of oral epithelium;
- Langerhans cells are present throughout oral epithelium (except junctional epithelium) and are characterized by the presence of Birbeck granules. They appear simultaneously with melanocytes and have limited proliferation. It originates in bone marrow and also transits outside the epithelium, being able to activate T lymphocytes;
- Merkel cells can be found in basal layer of oral epithelium and are characterized by the presence of small vesicles in cytoplasm, sometimes adjacent to a nerve fiber. These vesicles harbor a neurotransmitter, released in response to mechanical stimuli, triggering a nerve impulse;
- Inflammatory cells are infiltrated located between keratinocytes of oral epithelium. They have a transitory character, as they do not reproduce, being largely represented by lymphocytes. Mast cells and neutrophils can also be found. [91,92,93]

An equilibrium relationship between epithelial cells is mediated by cytokines produced in keratinocytes. Cytokines modulate Langerhans cells function. These produce interleukin-I, which activates T lymphocytes in response to external aggression stimuli.[91,92,93]

Basement membrane represents the junction between epithelium and lamina propria, ensuring greater tissue resistance. It also represents an area of metabolic exchange between epithelium and connective tissue, since epithelium is avascular.[91,92,93]

Lamina propria is connective tissue that supports oral epithelium. It consists of cells, blood vessels, neural elements, elastic and collagen fibers, housed in extracellular matrix and can be divided into two layers:

- papillary layer (more superficial and thinny), consisting of loose connective tissue and many cells and;
- reticular layer (deeper and thicker), with dense connective tissue, due to its arrangement of abundant and thick collagen fibers.

On lamina propria are found:

- Fibroblasts: main cell line of lamina propria, responsible for maintaining tissue integrity; secrete the precursors of collagen, elastin, proteoglycans and glycoproteins that make up the extracellular matrix. They are characterized by high proliferation during healing processes and, in this process, some of them differentiate into myofibroblasts, carrying intermediate characteristics between fibroblasts and smooth muscle cells;

- Macrophages: cells whose cytoplasm harbors lysosomes, whose main function is the phagocytosis of damaged tissue or foreign material. They originate from monocytes;

- Mast cells: mononucleated cell, which contains large amounts of histamine and heparin. Histamine is known to initiate the vascular phase of an inflammatory process;

- Inflammatory cells: cells mediate inflammation process. They appear associated with cells such as neutrophils, eosinophils, lymphocytes, plasma cells, monocytes and macrophages.

Extracellular matrix is composed of a set of macromolecules produced by cells themselves and determines physical and functional properties of tissues. Its fibrillar components are structural and adhesion proteins. Collagen and elastin represent structural proteins, conferring respectively, tensile strength and elasticity to tissue. Adhesion proteins, on the other hand, promote bonding of cells to matrix elements. Laminin binds epithelial cells to basement membrane and fibronectin binds fibroblasts to extracellular matrix. Non-fibrillar components, such as glycosaminoglycans and proteoglycans, promote hydration of the environment, allowing diffusion of nutrients, metabolites and hormones between blood vessels and cells, in addition to providing compressive strength to tissues. [91,92,93]

Collagen is the main component of extracellular matrix and corresponds to 25% of all protein in the body. In many tissues, they appear elongated and grouped in parallel arrangement, forming bundles of collagen fibers. Spatial arrangement of collagen molecule is in a triple helix. Each of them is made up of aminoacids.[91,92,93]

Oral mucosa can be subdivided into: masticatory, lining and specialized.

Masticatory mucosa covers the hard palate and gingiva, which are exposed to mechanical forces during mastication. It consists of keratinized stratified squamous epithelium. Elongated papillae provide good mechanical attachment to epithelium. Lamina propria is thick and contains a robust net of collagen fibers, making tissue more resistant. It is fixed by mucoperiosteum, since it does not have a submucosa layer.[91,92,93]

Lining mucosa may be thicker than masticatory mucosa and is not keratinized. Its flexible constitution can withstand strain; papillary interdigitations are smoothed. Lamina propria is thicker and has a smaller number of collagen fibers, which are irregularly arranged. Along these are elastic fibers that control the extent of mucosal extension. Lining mucosa protects:

- soft palate (with a highly vascularized lamina propria; it has projections of conjunctival papillae project to epithelium; in submucous region there are skeletal striated muscle fibers);
- tongue ventral surface;
- mouth floor;
- alveolar mucosa;
- mucosa of cheeks and lips;
- lips: red border and intermediate zone.

Lining mucosa is composed of a thin layer of epithelium, with an adjacent lamina propria. Its non-keratinized epithelium is presented in three distinct layers:

- Basal stratum (with basal layer of cubic cells);
- Intermediate stratum or spinous layer (oval in appearance and slightly flattened);
- Superficial stratum (with flat cells, many with a small oval nucleus). [91,92,93]

Figure 16 – Histological section: the oral mucosa of the soft palate region.
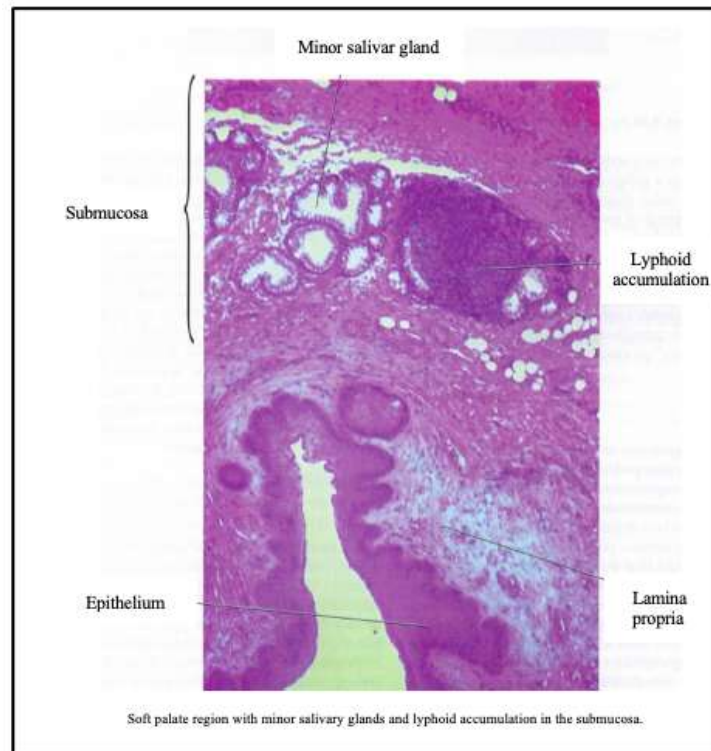
Source: Katchburian E, Chavez A, Elias V. Oral histology and embryology: text, atlas, clinical correlations. Rio de Janeiro: Guanabara-Koogan; 2004.

Specialized mucosa has many papillae, with mechanical and sensory functions. The tongue base contains lingual tonsils, which are composed of lymphoid tissues. Papillae that appear on the dorsum of the tongue are fungiform, filiform, foliate and circumvallate. Mucosa lining covers back of the tongue is exposed to food friction and therefore, it has keratinized epithelium. [91,92,93]

4.3.1 Healing process

Healing response begins shortly after injury and comprises four main phases: hemostasis, inflammation, proliferation, and remodeling.

First phase, hemostasis, is triggered by bleeding. At beginning, vasoconstriction occurs, which is followed by platelet activation, forming a clot, which corresponds to an initial matrix framework, rich in growth factors (which recruit cells for other healing stages).

In inflammatory phase, recruitment of immune cells occurs. Platelets, neutrophils and monocytes, differentiate into macrophages, contributing to cytokines and growth factors secretion.

In proliferation phase, reconstruction of injured site occurs, lasting up to 3 weeks, characterized by formation of abundant and vascularized granulation tissue, through

deposition of ECM by fibroblasts (composed mainly of type III collagen). Keratinocytes and endothelial cells are then recruited and activated at the injured site, promoting reepithelialization and neovascularization. Fibroblasts transit at wound site to an activated state, myofibroblasts, contributing to ECM deposition and allowing wound closure by contraction.

The last and longest phase of healing is remodeling. It starts around the 3rd week and can last for more than 1 year. During this phase, type III collagen is actively remodeled to type I collagen by fibroblasts, macrophages, and endothelial cells. This rearrangement of collagen fibers allows the new area to become more resistant, and scar thickness reduces over time.[91,92,93]

4.4 Contraindications and side effects of non-ablative treatments with Nd:YAG and Er:YAG lasers for SDB

As absolute contraindications for the use of Er:YAG and Nd:YAG lasers, it is mentioned:

- Present history of histologically demonstrated malignancy;
- Clinical findings indicative of malignancy;
- Epilepsy;
- Cases of active systemic infection;
- Exposure of retina to laser radiation;
- Pregnancy (although laser does not physically impact pregnancy, most manufacturers exclude the use of their equipment on pregnant women in their application notes. In most situations, laser treatment can be delayed until after delivery).[97]

Currently, there is no evidence to indicate non-ablative laser treatments are deleterious. Specifically, thermal injury after laser treatment can induce an inflammatory response. Recruitment of inflammatory cells and their release of cytokines can result in tissue remodeling.[94,96]

Non-ablative laser treatments involve a wide range of parameters, each of which has potential to influence the incidence of adverse events. An adverse event is any undesirable effect, even if expected, that results from a treatment. This, combined with

relative scarcity of published data on the subject, makes it difficult to effectively assess incidence rates of adverse events in non-ablative treatments. Professional awareness of the possibility of complications when using these techniques allows the delivery of desired results, minimizing risk to patients. Thus, factors related to patient, equipment, technique used and professional skill must be observed.[94]

4.4.1 Patient-related factors

Patient medical history should be analyzed and clinical conditions such as bacterial, viral and fungal infections of the treatment area (herpes simplex virus); connective tissue abnormalities (photosensitivity marker); abnormal keloids or scarring, post-inflammatory hyperpigmentation, family history of pigmentary abnormalities and systemic or local autoimmune disorders are contraindications to treatment. They must have clinical resolution prior to laser treatment.[95,97]

Reviewing patient medication in the last 6 months and their history of allergies are also essential to avoid or minimize side effects. Problem medications include retinoids (vitamin A), minocycline, gold, iron, amiodarone, warfarin, acetylsalicylic acid, niacin, nonsteroidal anti-inflammatory drugs, and vitamin E.[95]

4.4.2 Equipment-related factors

Current lasers, radio frequency devices and light-based sources are widely used by many professionals with varying degrees of training and experience. Most pulsed lasers adhere to the concept of selective photothermolysis in which thermal injury is spatially confined to tissue-specific chromophores and thermal damage to surrounding tissue is minimized. But there are devices that do not strictly adhere to selective photothermolysis principles, targeting chromophores that are not spatially confined, such as water around collagen, or when using non-coherent light and energy sources. Although these modalities are generally safe, incorrect or over-aggressive use of any laser or light device has the potential to generate postoperative complications.[94,95]

4.4.3 Technique used-related factors

Compared with ablative techniques, non-ablative treatment is less invasive, with shorter recovery time and fewer adverse effects. Use of proper technique is essential, due to absence of an immediate visible epidermal reaction to assess the response to treatment. Patient feedback on pain sensation is important during procedure and should be closely watched. Anesthesia is a risk factor for adverse events because patient perception of pain can be blunted and, as a result, excessive thermal damage may occur.[94,95]

Common side effects after non-ablative treatment include mild pain, erythema, and mild swelling. These usually disappear within a few hours after irradiation. Complications primarily result from tissue overheating and can include pain, tissue depigmentation, blisters, and scarring. Treating with lower fluences and multiple passes at appropriate parameters is advised to decrease risk of adverse events. Management of these adverse outcomes is largely supportive.[95]

As all vascular lasers are designed for greater depth of optical penetration and have strong absorption by hemoglobin, they have high potential for ocular damage (thermal destruction of retina and iris). Treatment in area close to the eye is not recommended unless eyes are covered with metal lenses and, adequate eye protection is mandatory for all persons within the operating room (including patient).[97]

Patients should be advised of reasonable expectations for treatment outcome. These changes can be subtle and clinically inapparent in some patients.[95,97]

4.4.4 Professional-related factors

Although some complications are laser related, many are still caused by operator error, either in consciousness or post-operative mismanagement.

When proper laser parameters and postoperative care are applied to appropriately chosen patients, the risk of complications remains low.

Thus, operator education and experience are essential to provide appropriate treatment, prevent adverse outcomes, and manage complications that may occur.[94,95,97]

5 METHODS

5 METHODS

5.1 Experimental design, time, study site, sample and current scenario

From the study question: "Does non-ablative treatment of sleep breathing disorder with high-intensity pulsed lasers enlarge upper airway lumen, facilitating air passage during breathing, in an outpatient procedure? Does the treatment result lead to improved sleep quality, snoring disorder and daytime sleepiness analyzed? Does it contribute to health parameters improvement observed through the tests performed?", the gold standard study design was sought to demonstrate effectiveness of an intervention in health investigations – longitudinal, interventional study, with prospective data collection – a controlled, randomized, double-blind clinical trial (patient and independent evaluators for analysis of the study main outcome), in order to eliminate possible sources of bias. Statistical analysis was performed by an independent evaluator blinded to the study.

Research was carried out at the Nuclear and Energy Research Institute (IPEN). Patients were seen for this study, in three sessions of 20 to 30 minutes ,14-days apart, at Fotona Brasil headquarters, at Rua Desembargador Eliseu Guilherme, 69 – Paraíso, São Paulo. Patients were followed up, with data collection for recording outcome measures at four times: before laser treatment, after laser treatment, 3-months and 6-months follow-up after laser treatment.

Oropharyngeal region of thirty volunteers aged between 25 and 65 years who were transitioning between primary snoring and moderate obstructive sleep apnea was treated with a high-intensity non-ablative sequence with two pulsed lasers Nd:YAG and Er:YAG, at 0, 14 and 28 days.

Primary snoring and obstructive sleep apnea are considered different severity degrees of the same disease – sleep breathing disorder – of chronic, complex and progressive nature, which affects about one billion people worldwide. Brazil has approximately 50 million apneic people. Early identification and correct management can reduce cardiovascular risk, emergence of chronic diseases and use of medications, which would represent important savings for healthcare organizations around the world, in addition to improving patients quality of life.

5.2 Study population

Thirty-two patients with clinical status compatible with SBD (between primary snoring and moderate obstructive sleep apnea), observed in polysomnography, with treatment initiated by the use of a mandibular advancement device, CPAP or not, who met eligibility criteria of the study in question, were included. Nevertheless, two of them were excluded after work started because they could not attend follow-up sessions. Thus, 30 patients were analyzed.

We considered untreated participants to be those who were aware of their health condition, the risks inherent to it, as well as therapeutic options for treatment and who decided not to adhere to them or even abandoned them on their own, after some unsuccessful attempt. Study was carried out in accordance with the Declaration of Helsinki, after approval by the Research Ethics Committee of the University of São Paulo Dentistry Faculty (CEP FOUSP CAAE: 44068621.8.0000.0075) and signing of the informed consent form (ICF). The CEP approval letter and the ICF can be found in annexes 1 and 2 of this dissertation.

5.2.1 Inclusion criteria

- Patients with clinical status compatible with primary snoring, mild or moderate obstructive sleep apnea, and polysomnography;
- Minimum 6-months washout for participants who had previously tried and given up on other treatment modalities;
- Age between 25 and 65 years;
- Both sexes and regardless of color or social class;
- Agreement and signature of the Informed Consent Term (Annex 1).

5.2.2 Exclusion criteria

- be under 25 years of age or over 65 at the start of survey;
- having significant physical obstruction of nostrils and/or throat observed by physician with strict indication for surgery and those with laryngeal obstruction;
- having previously performed surgery in oropharynx region;
- patients using more than two antihypertensive drugs or with previous diagnosis of heart problems;
- withdrawal of the Informed Consent Form;

- patients using photosensitive medication;
- presence of oropharyngeal lesion;
- alcohol and/or drug abuse;
- smokers;
- neurological or psychiatric disorders;
- craniofacial malformations;
- pregnancy or lactation;
- BMI above 40kg/m^2;
- patients who were unable to attend treatment sessions or follow-up appointments.

5.2.3 Number of research participants – N

Thirty-two study-blinded participants were randomized and blocked into two study groups: experimental and control. Two patients could not complete the follow-up appointments and were excluded from study. Thus, for analysis of results, N = 30 was considered.

5.3 Use of control group and ethics in research

- All patients were invited to participate in research, received explanations about the study and signed the informed consent;
- Both groups were followed up for outcome assessment. Data for evaluation were collected before and after intervention and also at 3-months and 6-months follow-up;
- Comparator: control group, which did not actually receive intervention, as the laser energy was not delivered, was clinically monitored during the research period, to assess the variability of outcome measures over time – odds ratio (OR). At the end of this study, with a positive intervention outcome, patients can receive treatment if they want it;
- Study was carried out in accordance with Declaration of Helsinki, after approval by the Research Ethics Committee of the Faculty of Dentistry of the University of São Paulo (CEP FOUSP CAAE: 44068621.8 .0000.0075) and signing the informed consent form. Patients identity, secrecy and confidentiality were preserved throughout

the research period. Only participants and their companions had access to results. Data will be published without exposing participants personal information.

5.4 Participant search and selection strategy

Individuals with history of primary snoring, mild or moderate obstructive sleep apnea were invited to participate in this research. Once included in study, participants were evaluated regarding their systemic health, through anamnesis questionnaire, on how they perceived their own snoring, on the presence of drowsiness during daily activities and sleep quality, through validated questionnaires for this purpose. At that moment, a type IV polysomnography exam was requested, to verify the compatibility between exam reading and clinical picture presented, and it served as a comparison parameter for evaluating the treatment result. Questionnaires used in the research can be found in annexes 3 to 6. Guidelines for carrying out polysomnography are in annex 7.

5.5 Randomization

Research participants were randomly assigned to two groups – control group and experimental group. All participants were informed about possibility of inclusion in any of the groups. Study was carried out on a block basis, according to the order in which patients volunteered. There were two study blocks – first with 20 participants and second with 12 participants. In blocks, participants were randomly assigned to each arm of the trial: control or experiment. In the first block, the first 10 patients who met study eligibility criteria were assigned to experimental group. The ten patients who presented themselves next, for control group. In the second block, the first 10 patients who met the study eligibility criteria were assigned to experimental group. The five patients who presented themselves next, to control group. At this point, due to arrival of the second Covid-19 pandemic wave, we stopped inviting patients. Three of patients assigned to control group at that time did not meet study eligibility criteria and were excluded.

- Group 1 – control: twelve patients – did not receive the treatment, which, showing positive in experimental group, will be offered to patients in this control at the end of study;

- Group 2 – experimental: twenty patients – received non-ablative treatmen with the association of two high-intensity pulsed lasers.

5.6 Intervention

High-intensity non-ablative sequential irradiation with two pulsed lasers, in oropharynx region, for treatment of SBD. Usual safety precautions related to instrument, biosafety and protection of operator, patient and assistant were followed. No pre-treatment medication or anesthesia was required under the irradiation conditions established in this study.

We used a laser system that integrates two wavelengths on the same platform – Nd:YAG (λ = 1064 nm) and Er:YAG (λ = 2094 nm) – LightWalker Fotona®, Slovenia, in three sessions of approximately 20 minutes, each 14 days.

Figures 17, 18 and 19 – Nd:YAG laser in use for the treatment of SBD and goggles, with detail of specifications for use.

Source: personal file of the author of this dissertation

In control group patients, only a guide light was used, without delivery of laser energy, during treatment.

Irradiation of selected area (soft palate, palatoglossal, palatopharyngeal arches and uvula) was performed perpendicularly to the tissue, at a working distance of 100 mm for

Nd:YAG laser and 20 mm for Er:YAG laser. Laser light was delivered punctually to treated regions, and is identified in blue in Figure 20. Six laser scans in each line, with four to five shots per dot, in each of the sequence five steps.

Figure 20 – Irradiated regions in the treatment of SDB and LightWalker Fotona® equipment.

Source: image provided by Fotona and adapted by the author of this dissertation

The laser beam was gradually moved until all areas were treated. Occasionally, patients experienced a sensation of intense heat in an irradiated region, without the need to interrupt treatment. Patients returned to their usual activities immediately, without any restrictions. The irradiation parameters are presented in table 2 and were defined in order to deliver energy safely and efficiently.

Table 2 – Irradiation parameters used in this work.

sequence	λ (nm)	*spot* (mm)	pulse width (ms)	power density (W/cm²)	energy per pulse (J)	repetition rate (Hz)	energy density per pulse (J/cm²)
1º step	1064	10	1.0	6.0	0.47	10	0.6
2º step	1064	10	1.0	12	0.47	20	0.6
3º step	2940	7.0	0.6	20	0.77	10	2.0
4º step	2940	7.0	300 *	7.5	1.92	1.5	5.0
5º step	2940	7.0	300 *	18	3.46	2.0	9.0

(*: a train of pulses lasting 300 milliseconds)

First, with Nd:YAG laser, for deeper tissue non-ablative thermal sensitization, 1064 nm wavelength, MarcCo S handpiece, 10 mm spot diameter, 100 mm away from tissue, with ED: 0.6 J/cm², 1.0 millisecond pulse width and 10 Hz rate of repetition, followed by another irradiation, the second step, at the same wavelength and repetition rate at 20 Hz.

Figure 21 and 22 – Irradiation of the oropharynx region with Nd:YAG laser and Marco S handpiece with coupled spacer; laser handpiece in detail.
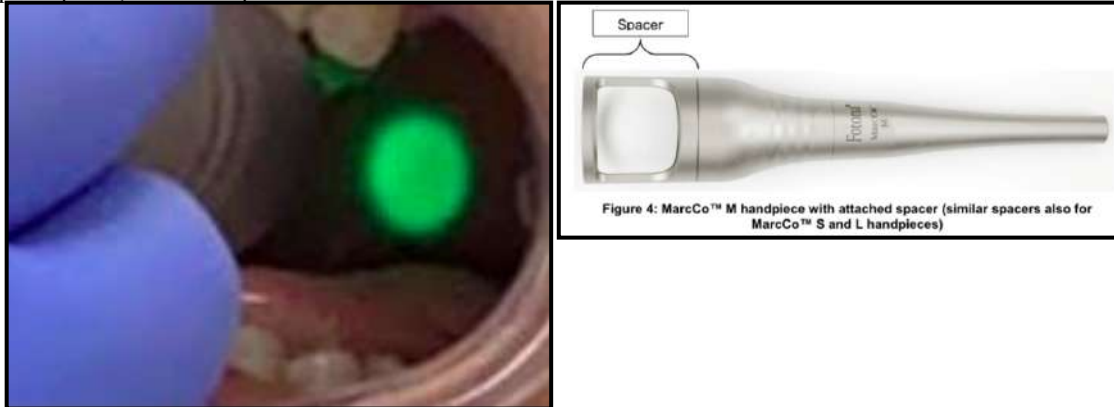
Source: personal file of the author of this dissertation and LightWalker Fotona owner's manual.

In the irradiation sequence third step, with Er:YAG laser, for superficial and non-ablative tissue treatment, 2940 nm wavelength, PSO4 handpiece with pixel screen optical technology, 7 mm spot diameter, 2 mm away from tissue, ED: 2.0 J/cm², 0.6 millisecond temporal width at 10 Hz repeat rate.

In the fourth step of irradiation, at the same wavelength, in pulse train mode (duration of 300 milliseconds), ED: 5.0 J/cm² and 1.5 Hz repetition rate. And in sequence, the fifth and last step, with same temporal width, the energy density was raised to 9.0 J/cm² at 2.0 Hz repetition rate.

Figure 23, 24 and 25 – Irradiation of the oropharynx region with Er:YAG laser and PS04 handpiece with pixel screen optical technology; handpiece in detail.
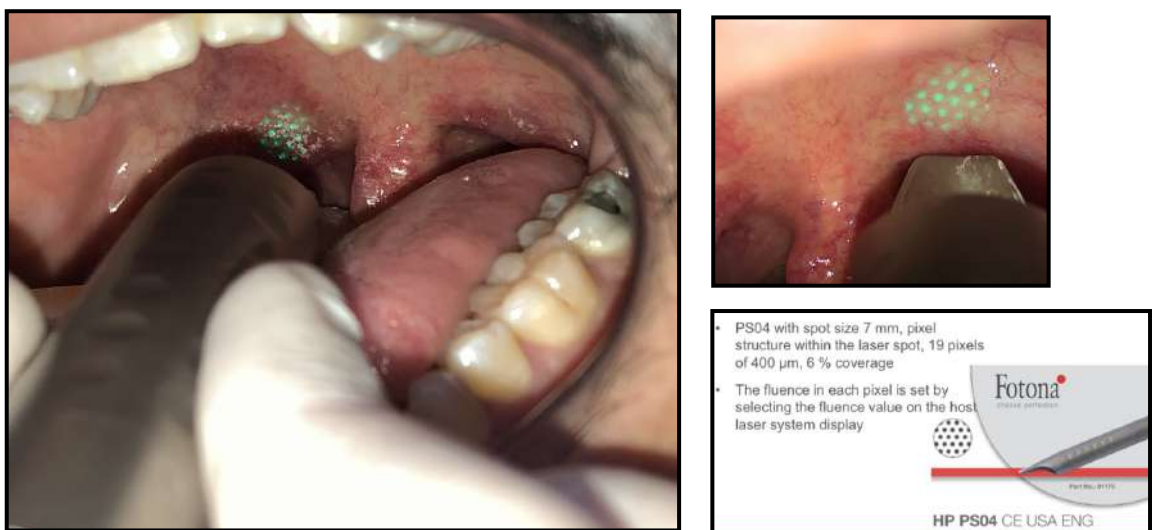
Source: personal file of the author of this dissertation and LightWalker Fotona owner's manual.

The number of pulses per session varied according to anatomical characteristics of each person.

5.6.1 Risks of participating in the research

We consider the present study could bring as a risk to research participants, therapy not having the desired effect or having a transitory effect. As discomfort, the report of local discomfort sensation, due to a light, but very brief heat sensation in the region received laser irradiation. The responsible researcher committed to suspend the research immediately when noticing any discomfort to research participant, resulting from study. Researchers and institution assumed the responsibility to provide comprehensive care for any complications and damages that might occur.

5.6.2 Benefits of participating in the research

The study evaluated non-ablative use of two high-intensity pulsed lasers and their benefit in treatment of SBD. Research participants had the possibility of having severity of oxyhemoglobin desaturation and snoring parameters reduced or eliminated, in addition to improving sleep quality. With positive results, in the future, this laser therapy may represent a new treatment approach for SBD, thus contributing to reduction of chronic diseases and medication use, in addition to contributing to improvement of sleep quality and, consequently, population quality of life.

5.6.3 Expected outcome

As the main clinical result, we tried to answer the research question: non-ablative treatment of SBD with high-intensity Nd:YAG and Er:YAG pulsed lasers, widens the lumen of upper airways (UA), facilitating air passage during breathing, in an outpatient procedure? Does the treatment result lead to improved sleep quality, snoring disorder and daytime sleepiness analyzed? Does it contribute to the improvement of health parameters observed through the tests performed?

5.7 Outcome measures

Outcome measures were performed by analyzing data records obtained at the end of treatment and also at return for follow-up at 3 and 6 months after the end of treatment and compared with those obtained at baseline.

Objective data:

- Oropharyngeal lumen space for breathing airflow passage recorded by photography of the mouth interior and classified according to modified Mallampati index, which establishes a relationship between tongue and soft palate. The modified form is validated as a predictor method for SBD severity and, according to Friedman et al, in an article published in 2013, the following graduation is observed:
  - Class I — the entire oropharynx posterior wall is visualized, including the inferior pole of palatine tonsils;
  - Class II — part of oropharynx posterior wall is visualized;
  - Class III — the insertion of uvula and soft palate are visualized, and oropharynx posterior wall cannot be seen;
  - Class IV — only part of soft palate and hard palate are visualized, as in Figure 26.[24]

Figure 26 – Illustration of upper airway (UA) lumen according to the different stages of modified Mallampati index.
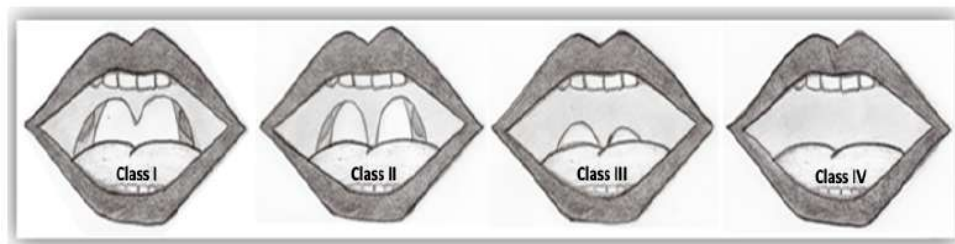
Source: personal file of author of this dissertation.

- Oxyhemoglobin desaturation index (ODI), saturation time below 90%, minimum and average oxyhemoglobin saturation during sleep and snoring time recorded by type IV polysomnography;
- Peak amplitude of snoring noise in decibels. Snoring sound, recorded on the same night that polysomnography was performed and analyzed by Adobe Audition

software. Peak amplitude of snoring noise (dB) was measured and served as a parameter for the outcome evaluation.

Self-reported data:

- Daytime sleepiness, sleep quality, patient perception of snoring recorded by validated questionnaires for these purposes.

5.7.1 Instruments for data collection and standardization of records

Sleep time with snoring, oxyhemoglobin desaturation index, saturation time below 90%, minimum and mean oxyhemoglobin saturation were obtained by high resolution oximetry and Biologix software, in a type IV polysomnography exam, validated by Anvisa and Incor for this purpose. The sound of snoring noise was recorded by a smartphone recorder on the same night that polysomnography examination was performed. Equipment was delivered to patient on that occasion for this purpose. Data were first stored in internal memory of Oxistar BX1 oximeter, which, at regular intervals of 5 minutes, sent them via bluetooth to smartphone. At the end of exam, data from the entire night sleep were transferred from smartphone to a web server, generating a type IV polysomnography report, with information from the entire night's sleep. The report of an examination, with data used as outcome measures, can be found in Annex 8.

To perform polysomnography exam, at all times of this study (from baseline to follow-up 6 months after the end of treatment), all patients were instructed to sleep in a room without a companion, after a light meal, using a positional band for lateral decubitus and pillow of adequate height, as a way of standardizing the performance of this examination.

Figure 27, 28, 29, 30 and 31 – Oximetry sensor and Biologix software, used in type IV polysomnography performed in this study, report on two pages of the type IV polysomnography, kit sent to all patients to perform the exam, containing a smartphone to record snoring, a high resolution oximeter and micropore tape for fixation, a positional band for lateral decubitus during the exam and eye protector (optional use); patient using the band during the sleep exam.

Source: personal file of the author of this dissertation.

The recording of snoring noise during sleep night in which polysomnography was performed was transferred by AirDrop to computer, where it was analyzed by Adobe Audition software. Environmental interference sounds in recording were not considered for reading the snoring noise peak amplitude. In the program waveform editor, panel provided a visual representation of sound waves, ideal for evaluating audio amplitude. The display of sound recorded during the night on panel, showed up as series of positive and negative peaks. X-axis (horizontal ruler) measured time and Y-axis (vertical ruler) measured amplitude, thus monitoring amplitude of snoring noise in decibels throughout the night. A printscreen record of this panel, with graphic representation of sound waves, evaluated in amplitude over time, and recording of the audio peak amplitude was performed to record noise magnitude reading and the measured value served as parameter for ending evaluation. A record of this panel can be found in Annex 9.

Figure 32 – Adobe Audition shape editor panel with visual representation of sound waves throughout the sleep exam.
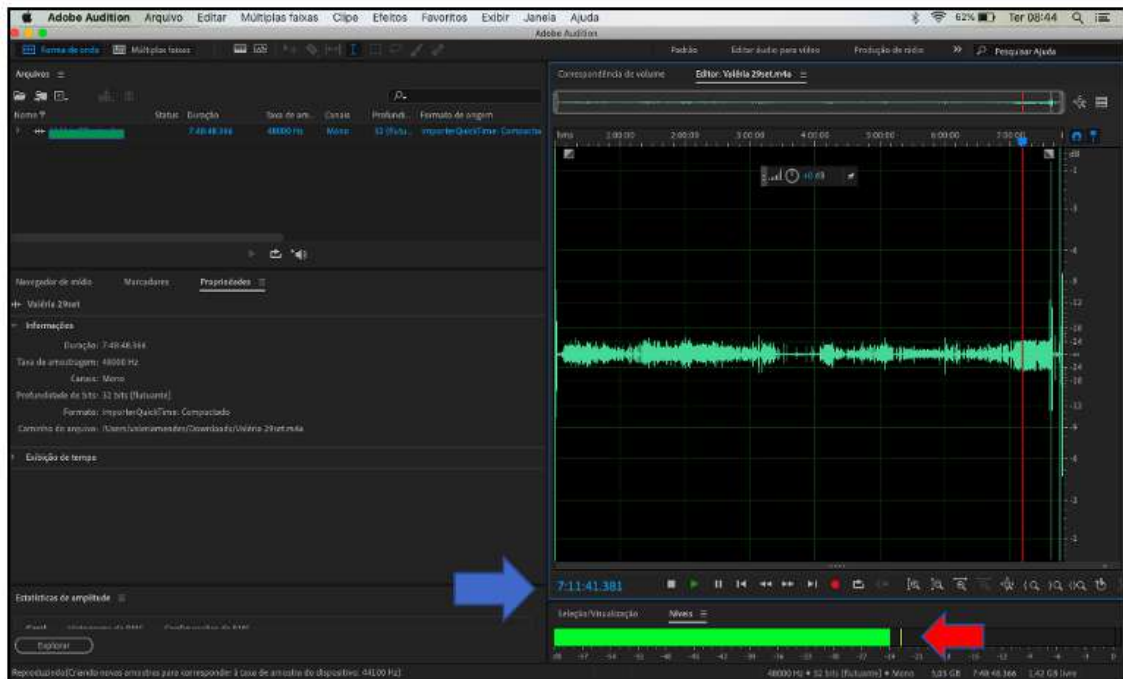
Source: personal file of the author of this dissertation. On the x axis, time and on the y axis, amplitude in decibels.

For upper airway lumen photographic record, image capture was performed by a smartphone camera. As standard, patient was seated with erect spine, mouth at maximum opening, lip retractor positioned, tongue resting on the mouth floor, with photographic record taken at the end of a slow and deep inspiration. Image obtained was classified according to modified Mallampati index, by visual comparison performed by main researcher and three independent evaluators, blinded and calibrated for this study.

Figure 33, 34 and 35 – Photographic record of upper airway lumen (UA) for classification according to modified Mallampati index.

Class I   Class II   Class III   Class IV
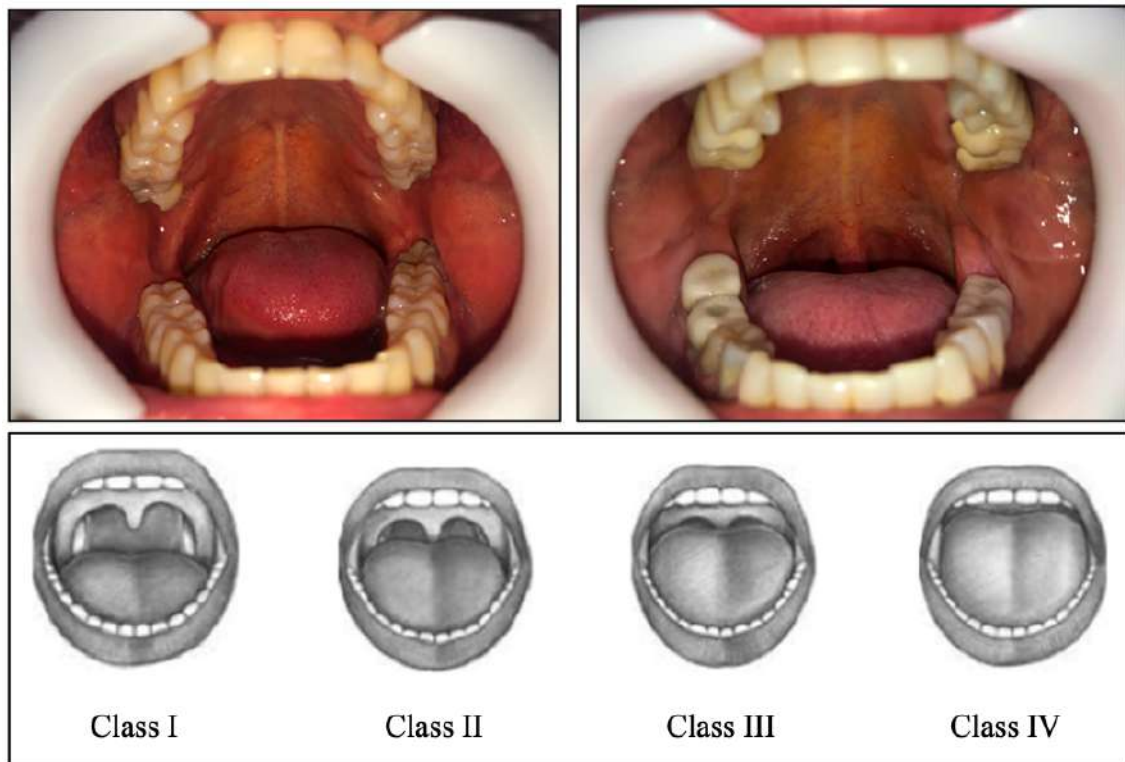
Source: personal file of the author of this dissertation and Friedman M, Hamilton C, Samuelson CG, Lundgren ME, Pott T. Diagnostic Value of the Friedman Tongue Position and Mallampati Classification for Obstructive Sleep Apnea: A Meta-analysis. Otolaryngology–Head and Neck Surgery. 2013;148(4):540-547.

Questionnaires to assess patient perception of daytime sleepiness, sleep quality and snoring severity were delivered at polysomnography exams time and results were recorded in a spreadsheet for further analysis.

5.7.1.1 Calibration of evaluators

According to a 2001 publication, examiner calibration – a consecrated expression used in epidemiology – represents process that aims to establish uniform standards for examination, determining acceptable parameters of internal and external consistency to examiners. Intra-examiner calibration verifies how much calibrator agrees with himself, regarding exam performed, at different times. Inter-examiner calibration evaluates same group of individuals and examiners evaluations are compared to verifying which examiners are differing most significantly, in order to reduce variability between them. One of requirements to ensure reliability of the findings is minimization of variation and diagnostic errors, using standardized criteria. Thus, the objective of calibration is to minimize errors and differences may exist in terms of ability to obtain data and judge them; ensure uniform

interpretation, understanding and application of criteria for diseases and conditions to be observed, recorded and that each examiner can examine within a consistent standard, minimizing variations between different examiners.[101,102,103]

Thus, evaluator calibration process, which followed a protocol adapted to the needs of this work, was essential to avoid bias (systematic errors) in observation of results. Steps included theoretical and practical training, practical exams and final verification of evaluators calibration.[101,102,103]

1st stage: Theoretical training

A. Review of applied indexes criteria and investigated results evaluation protocol, through a document prepared for this purpose and found in annex 10 of this dissertation.

B. Evaluation of evaluators knowledge: after exposing criteria for evaluating results, there was exposure of photographic records in different commitment degrees of evaluated conditions. For each photograph exposed, examiner had to fill out an evaluation form, with possibility of consulting written training material. Subsequently images were presented again to evaluators, in a new opportunity for analysis. At the end of process, images and their respective classifications were presented and discussed by responsible researcher. At that moment, doubts were clarified.

2nd stage – Practical training

In practical stage, information contained in research project was standardized and systematized. Responsible researcher explained how clinical data were collected. And evaluators training regarding adopted criteria was done through evaluation forms, allowing evaluators to become familiar with criteria adopted in research. Doubts were cleared at that time.

3rd and 4th stage – Practical exams and final verification of calibration between evaluators

Ten percent of the total study sample was analyzed by all evaluators, twice, at different times. Intraclass Correlation Coefficient test, used when variable is quantitative, was then applied, in order to assess the degree of agreement between the 1st and 2nd assessments.

The baseline limit of agreement was set at ≥ 80%. It was established these steps would be repeated until this degree of agreement was reached. Subsequently, entire study population was evaluated. There was no communication between examiners.[104,105]

Agreement between assessments ranges from 0 to 1, with values lower than 0.5 indicating poor agreement. Values between 0.5 and 0.75 indicate moderate agreement. Values between 0.77 and 0.9, good agreement and values above 0.9, excellent agreement.[101,103,104,105]

Data collected were tabulated into Microsoft Office Excel spreadsheet by the responsible researcher and, from this spreadsheet, statistical analysis was performed by an independent evaluator who was blinded to the study.

5.8 Statistical analysis

It was assumed at least 50% of patients treated with the combination of Nd:YAG and Er:YAG lasers would show changes in UA lumen (classified according to modified Mallampati index), while control group would have no change Thus, the sample calculation was based on an effect magnitude of 50%, assuming $\alpha = 5\%$ and sampling power of 80%. We imagined losses after randomization and adopted N = 45 as the study strategy.

Due to second pandemic wave of Covid 19 and with randomization at N = 32, the sampling power was recalculated to decide whether to postpone the research or continue with a sample of 32 patients. Data from two patients who dropped out of the study after being randomized were not included in statistical analysis.

OriginPro 2020 SR1, version 9.7.0.188 (OriginLab Corporation, Massachusetts, USA), Minitab 2022, version 21.2 (Minitab LLC, Pennsylvania, USA) and Stata version BE 17.0, updated October 10, 2022 (StataCorp LCC, Texas, USA software) were used.

5.8.1 Sample Power

The power of the sample was tested using the Modified Mallampati Scale to be the main outcome variable of the study. The Poisson Rate Test for 2 Samples was used, with a significance level of $\alpha = 5\%$.

Data from the period between Post and Basal were used, already classified as "Reduced" or "Not Reduced". The proportion of "Reduced" in the Control group was, on average, 20% compared to the Experiment group. In this way, the power of the sample for an

N = 12 is above 80%, as can be seen in the image below. The potency was maintained in the other periods.

Figure 36 – Sample Power Curve using the Modified Mallampati Index in the period between Post-treatment and Basal.
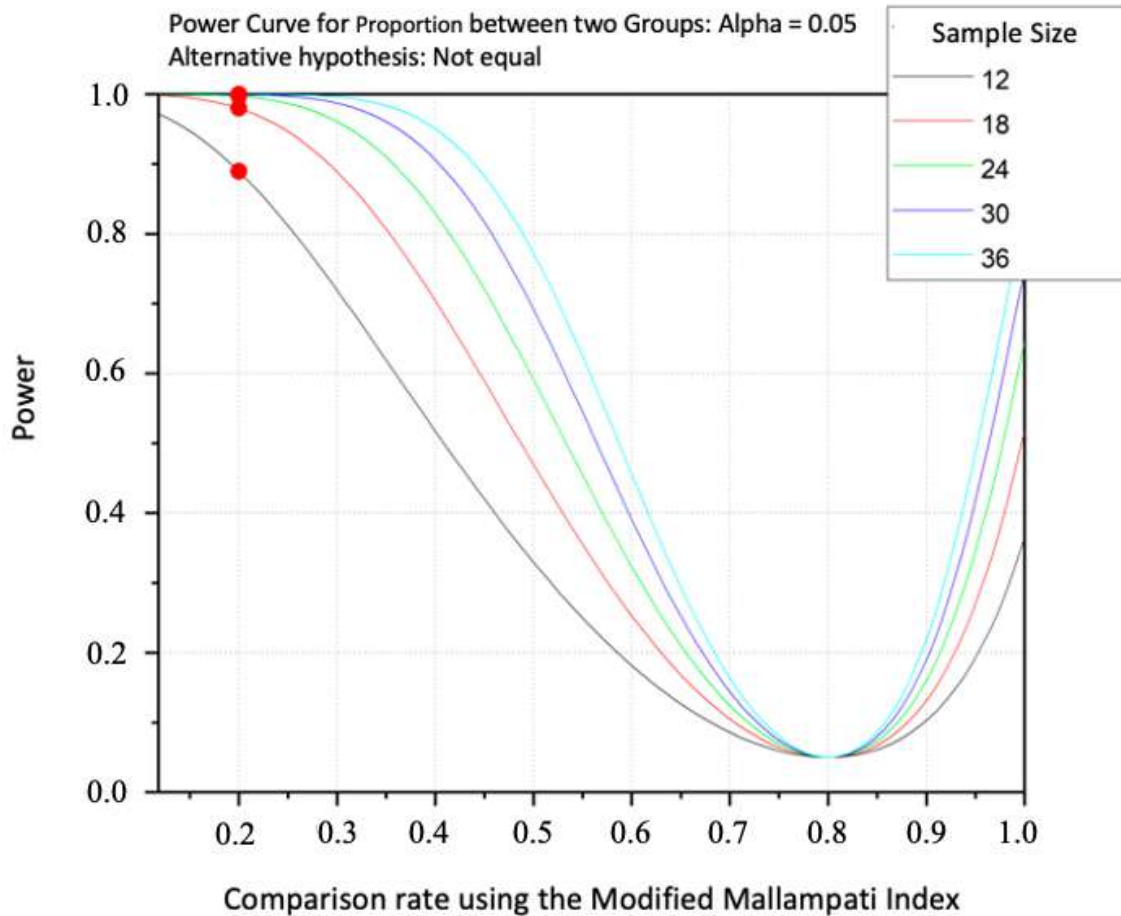
Source: personal file of the author of this dissertation. The different colors represent estimates for different sample sizes.

5.9 Follow-up time

Follow-up of research participants took place from pre-care moment, performing baseline exams, before laser treatment, until the return session for a 6-months follow-up.

5.10 Evaluation of results

Evaluation of results was carried out by method of comparing data with baseline record. Three independent evaluators, blinded and calibrated for study evaluation, analyzed

data collected to evaluate the main outcome (UA lumen analysis, according to modified Mallampati index classification).

The medians of age and BMI demographic variables were compared using the Mann-Whitney test, with a significance level of $\alpha = 5\%$. Values represented by median ± interquartile range. The probability that the detected difference occurred by chance is the value represented by p.

The distribution of frequencies between men and women of the variable Gender, between classes I and II of the Occlusal Pattern, between the Atresic and Normal classes of the Hard Palate, between the Elongated, Thick Elongated, Thick and Normal classes of the Soft Palate, between the classes Mild OSA, Moderate OSA, PR and UARS of the Clinical Status were compared using the Chi-Square test with a significance level of $\alpha = 5\%$.

Evaluators calibration process followed a protocol adapted to the study needs and was essential to avoid observation bias in the results. The baseline limit of agreement was set at $\geq$ 80%.

Data obtained from study population by evaluators were tabulated and followed for statistical analysis. The agreement between evaluators analysis was performed using Intraclass Correlation Coefficient (ICC) test, because the variables of interest are quantitative. The algorithm used was the Mixed two-way/Consistency of agreement, since the evaluators were not chosen randomly, unlike the patients. Significance $\alpha = 5\%$ was adopted. Results were represented by the ICC value and its respective 95% confidence interval. Four evaluators and 30 patients were analyzed.

Evaluator 3 was chosen to perform the comparison between the groups due to its better performance among the evaluators, according to the Intraclass Correlation Coefficient (ICC) test, described above. However, first, the variation between periods was calculated according to the following formula:

Equation 1

Thus, it was possible to analyze the difference between the periods in relation to baseline for each variable, both immediately after treatment and after 3 and 6 months.

Then, the classification "Reduced" or "Not Reduced" was assigned to the above variation, making it possible to apply the Fisher-corrected Chi-Square test, with a significance level of $\alpha = 5\%$.

6 RESULTS

6 RESULTS

Study followed according to flowchart shown in Figure 36.

Of 35 candidates who volunteered, 32 met study eligibility criteria. Two patients were excluded from study because they did not attend follow-up visits. None of patients treated required anesthesia or medication. Two patients reported feeling intense heat during irradiation, with no need to interrupt irradiation. One patient reported a dryness sensation in the throat, which resolved spontaneously. Six patients reported a noticeable improvement in breathing immediately after first irradiation. There was no evidence of epithelium integrity disruption in any patient seen in this study.

Figure 37 – Flowchart representing the work methodology.
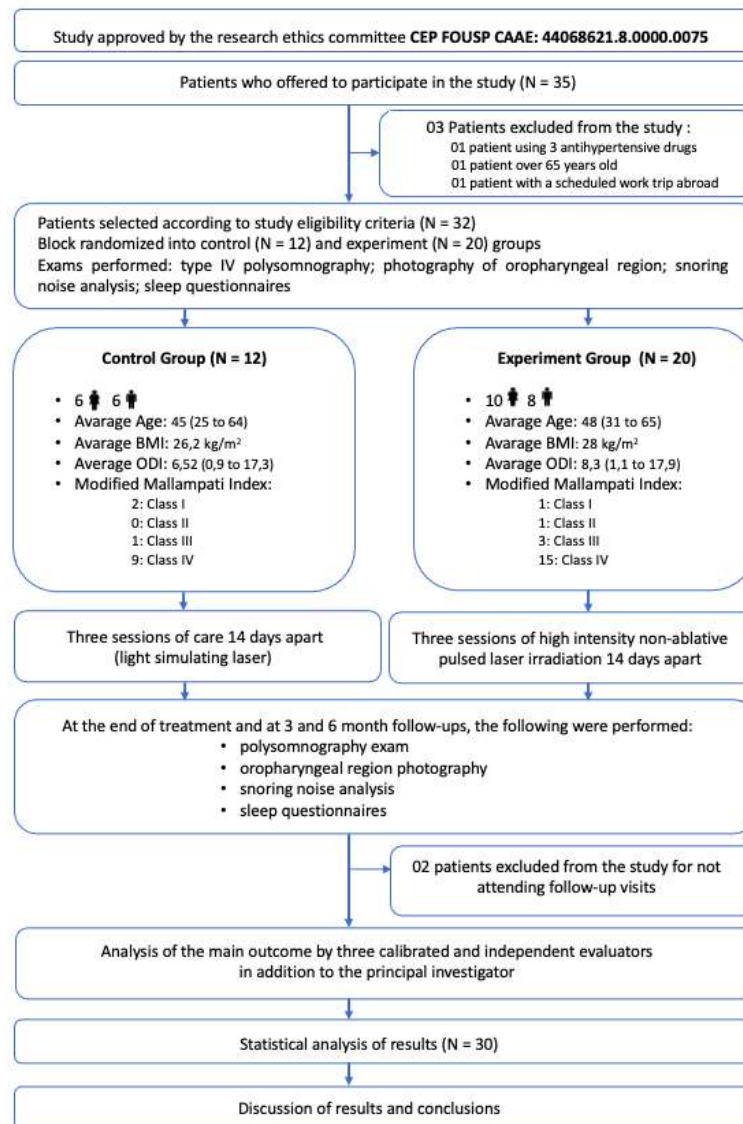
Source: personal file of the author of this dissertation.

6.1 Demographic and anthropometric data of the population studied

The medians of age and BMI demographic variables were compared using the Mann-Whitney test, with a significance level of $\alpha = 5\%$.

Control group (A) had 12 participants with mean age of 45 years and mean BMI of 26.2 kg/m². Experimental group (B) had 18 participants with mean age of 48 years and mean BMI of 28 kg/m².There was no difference in age (p = 0.56370) or BMI (p = 0.99999) between groups of the studied population. Data are presented in table 3.

Table 3 – Demographic and anthropometric data of each group.

	A (control N = 12)	B (experimental N = 18)	P (value)
Age (Years)	45.0 ± 15.5	48.0 ± 9.0	0.56370
Body Mass Index(BMI)	26.2 ± 7.4	28.0 ± 7.3	0.99999

Age and BMI: values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

Distribution of frequencies between men and women of the variable Gender, between classes I and II of the Angle Occlusal Pattern, between the Atresic and Normal classes of Hard Palate, between the Elongated, Elongated Thick, Thick and Normal classes of Soft Palate, between classes Mild OSA, Moderate OSA and PS of the Clinical Status were compared using the Chi-Square test with a significance level of $\alpha = 5\%$. There was no significant difference in any of the demographic variables, as shown in table 4.

Table 4 – Absolute frequency of other demographic and anthropometric variables.

	A (control)	B (experiment)	P (value)
Gender			0.76509
Male	6	8	
Female	6	10	
Angle Occlusal Pattern			0.23527
I	10	10	
II	2	8	
Hard Palate			0.62208
Atresic	1	4	
Normal	11	14	
Soft Palate			0.13915
Elongated	4	6	
Elongated Thick	1	8	
Thick	1	0	
Normal	6	4	
Clinical Status			0.55200
Mild OSA	3	8	
Moderate OSA	2	2	
PS	7	8	

OSA: Obstructive sleep apnea. PS: Primary snoring. Values represented by the absolute frequency. The probability the detected difference occurred by chance is the value represented by p.

6.2 Evaluators Concordance Analysis

Analysis of agreement between the evaluators for the study main outocume was performed using the Intraclass Correlation Coefficient (ICC) test because the variables of interest are quantitative. The algorithm used was the Mixed two-way/Consistency of agreement, since the evaluators were not chosen randomly, unlike the patients. Significance α = 5% was adopted. Results were represented by the CCI value and its respective 95% confidence interval. Four evaluators and 30 patients were analyzed.

When comparing the modified Mallampati index between evaluators before treatment, agreement was 0.84 (0.75 – 0.91) for single measures and 0.96 (0.92 – 0.98) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 1 was 0.93 (0.86 – 0.97) for single measures and 0.96 (0.92 – 0.98) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 2 was 0.65 (0.38 – 0.81) for single measures and 0.79 (0.55 – 0.90) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 3 was 0.97 (0.93 – 0.98) for single measures and 0.98 (0.96 – 0.99) for average measures, with p < 0.001.

When comparing the modified Mallampati index between evaluators after treatment, agreement was 0.90 (0.83 – 0.94) for single measures and 0.97 (0.95 – 0.99) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 1 was 0.91 (0.83 – 0.96) for single shares and 0.95 (0.91 – 0.98) for medium shares, with p < 0.001.

The agreement between evaluators Mendes V and 2 was 0.83 (0.67 – 0.91) for single shares and 0.91 (0.80 – 0.96) for medium shares, with p < 0.001.

The agreement between evaluators Mendes V and 3 was 0.95 (0.89 – 0.97) for single shares and 0.97 (0.94 – 0.99) for medium shares, with p < 0.001.

When comparing the modified Mallampati index between evaluators 3 months after treatment, agreement was 0.93 (0.88 – 0.96) for single measures and 0.98 (0.97 – 0.99) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 1 was 0.94 (0.88 – 0.97) for single measures and 0.97 (0.94 – 0.99) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 2 was 0.88 (0.76 – 0.94) for single measures and 0.94 (0.87 – 0.97) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 3 was 0.98 (0.96 – 0.99) for single measures and 0.99 (0.98 – 1.00) for average measures, with p < 0.001.

When comparing the modified Mallampati index between evaluators 6 months after treatment, agreement was 0.92 (0.84 – 0.96) for single measures and 0.98 (0.95 – 0.99) for average measures. , with p < 0.001.

The agreement between evaluators Mendes V and 1 was 0.93 (0.84 – 0.97) for single measures and 0.97 (0.91 – 0.99) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 2 was 0.86 (0.56 – 0.95) for single measures and 0.93 (0.72 – 0.97) for average measures, with p < 0.001.

The agreement between evaluators Mendes V and 3 was 0.99 (0.98 – 1.00) for single measures and 1.00 (0.99 – 1.00) for average measures, with p < 0.001.

At all times of the study, baseline ICC limit was higher than the pre-established 80%. Best agreement between evaluators occurred at "3-months return" moment [0.93 (0.88 – 0.96) for single measures and 0.98 (0.97 – 0.99) for average measures, with p < 0.001] and worst, at "before irradiation" moment [0.84 (0.75 – 0.91) for single measurements and 0.96 (0.92 – 0.98) for average measurements, with p < 0.001], as shown in table 5.

Table 5 – Calibration between evaluators: establishment of agreement.

	UNIQUE MEASURES	AVERAGE MEASUREMENTS	p (value)
Agreement between evaluators – before irradiation	0.84 (0.75 – 0.91)	0.96 (0.92 – 0.98)	p < 0.001
Agreement between evaluators – after irradiation	0.90 (0.83 – 0.94)	0.97 (0.95 – 0.99)	p < 0.001
Agreement between evaluators – 3 months return	0.93 (0.88 – 0.96)	0.98 (0.97 – 0.99)	p < 0.001
Agreement between evaluators – 6 months return	0.92 (0.84 – 0.96)	0.98 (0.95 – 0.99)	p < 0.001

Single measures mean agreement between raters for the same patient. Mean measurements mean agreement between raters in relation to the mean value attributed to a patient. The probability the detected difference occurred by chance is the value represented by p.

Figure 38 – Scatter matrix of UA lumen ratings according to the Modified Mallampati index by the 4 study evaluators.
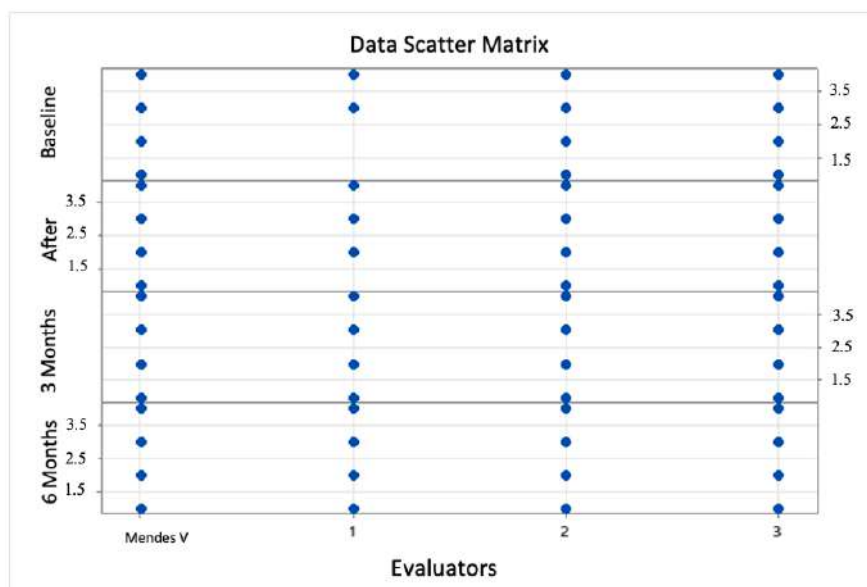
Source: personal file of the author of this dissertation.

6.3 Main outcome of the study: analysis of UA lumen by Modified Mallampati Index between groups, in each of the periods.

Evaluator 3 was chosen to perform the comparison between the groups due to its better performance among evaluators, according to Intraclass Correlation Coefficient (ICC) test, described above.

According to table 6, control (A) and experiment (B) groups were homogeneous in terms of patient distribution classified by modified Mallampati index before treatment (p=0.80096). However, there was a difference after treatment (p = 0.00258), as well as in return for 3 and 6 months follow-up (p = 0.00641 and p = 0.01432, respectively).

Table 6 – Modified Mallampati index for each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	4 ± 1	4 ± 1	4 ± 1	4 ± 1	0.99925
B (experiment)	4 ± 0	2 ± 2	2 ± 3	2 ± 3	0.01681
p (value)	0.80096	0.00258	0.00641	0.01432	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p. The significance detected in group B (p = 0.01681) was between the period Before and After (p = 0.00334), between Before and 3 Months (p = 0.00536) and between Before and 6 Months (p = 0.00786).

Control group (A) showed no difference in patients distribution classified by modified Mallampati index at different times of the study (p = 0.99925).

Experimental group (B) showed a difference after irradiation and difference was sustained in return for 3 and 6 months after the end of treatment follow-up (p = 0.01681).

In order to show occurrence of change between the analyzed periods, first, the variation between periods was calculated according to the following formula:

Equation 1

Thus, it was possible to analyze the difference between periods in relation to baseline for each variable, both immediately after treatment and after 3 and 6 months after that. Then, classification "Reduced" or "Not Reduced" was assigned to the above variation, making it possible to apply the Fisher-corrected Chi-Square test, with a significance level of $\alpha = 5\%$.

There was a significant difference between the groups in all periods, as can be seen in the figure below.

Figure 39 – Modified Mallampati index variation of each group in different experimental periods.
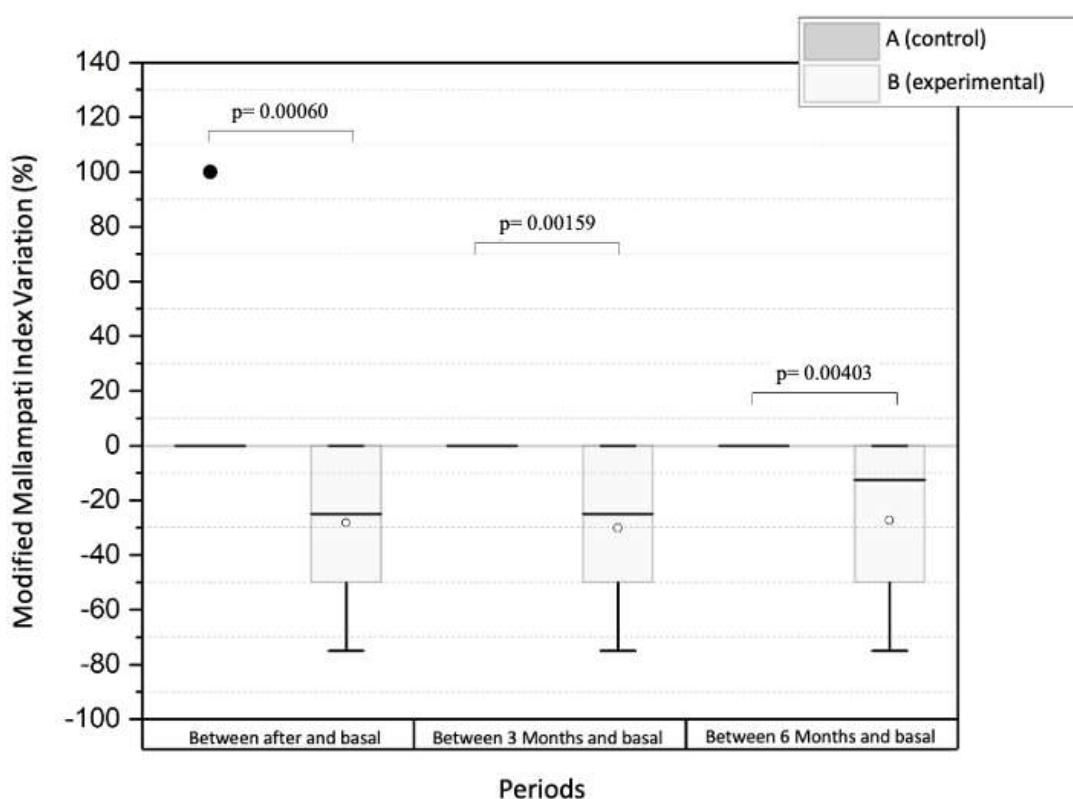
Source: personal file of the author of this dissertation.

Table 7 – Modified Mallampati Index rate variation of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variation between "3 months and Basal" (%)	Variation between "6 months and Basal" (%)	p (value)
A (control)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.36788
B (experimental)	-25.0 ± 50.0	-25.0 ± 50.0	-12.5 ± 0.0	0.88250
p (value)	0.00060	0.00159	0.00403	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

Clinically, change in standard classification can be observed in the figures sequences 40 and 41.

Figure 40 and 41 – Sequence of modification in the Mallampati classification pattern of two clinical cases, at different times of the study.
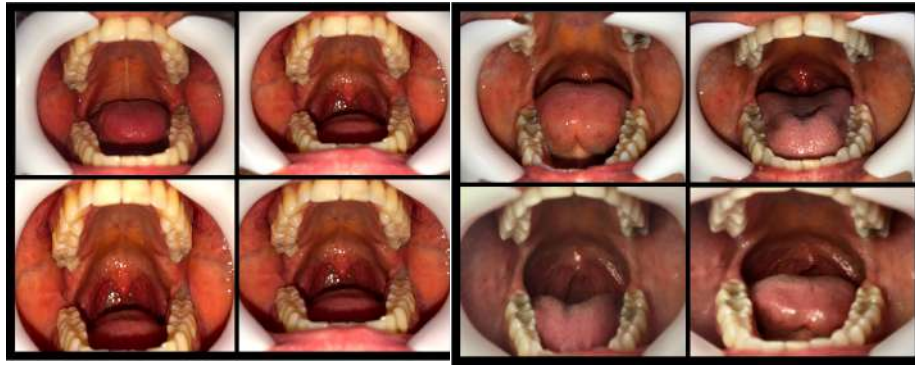
Source: personal file of the author of this dissertation.

6.4 Secondary outcomes

The same formula (Equation 1) was used to determine the variation between the analysis periods for all secondary outcome variables. Then, classification "Reduced" or "Not Reduced" was assigned to the above variation, making it possible to apply the Fisher-corrected Chi-Square test, with a significance level of $\alpha = 5\%$. Thus, it was possible to analyze difference between the times, in relation to baseline for each variable, both immediately after treatment and 3 or 6 months after that. Results were represented by median value and its respective interquartile range.

6.4.1 Oxyhemoglobin Desaturation Index (ODI)

There was a difference between the groups when the variation rate between the "After and Baseline" ($p = 0.018$) and "3 months and baseline" ($p = 0.019$) was verified.

Figure 42 – ODI variation of each group in the different experimental periods.
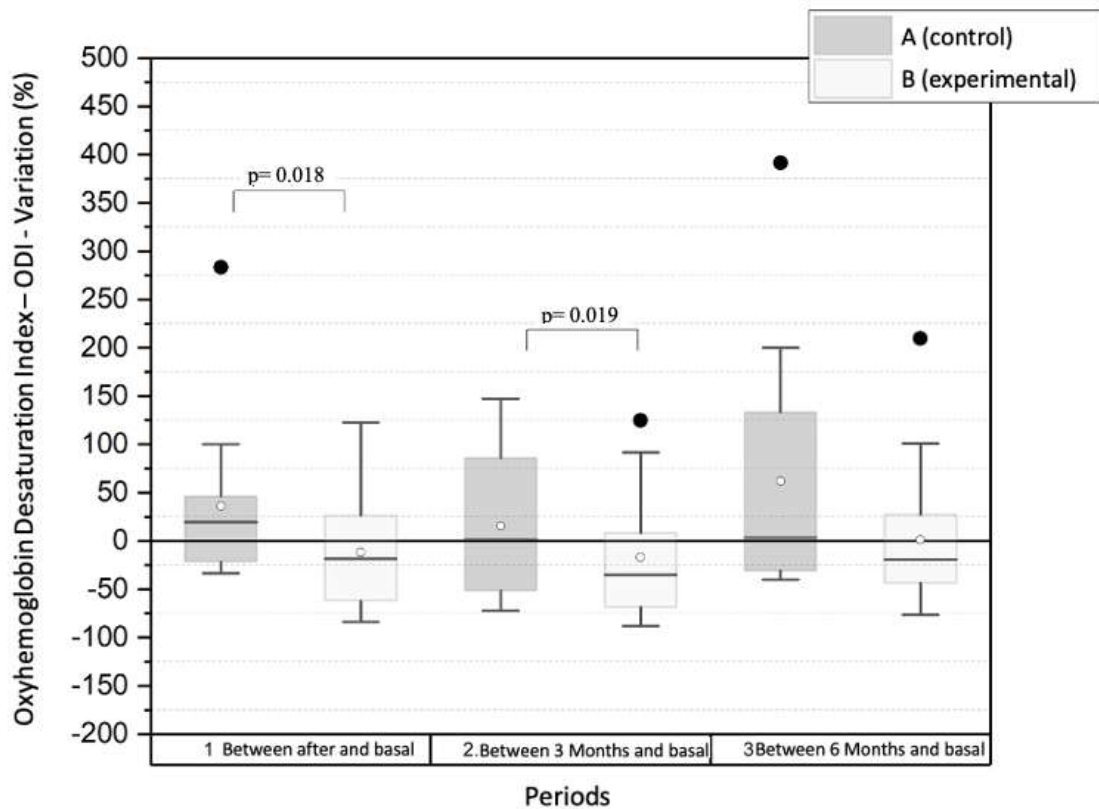
Source: personal file of the author of this dissertation.

Table 8 – ODI rate variation of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variation between "3 months and Basal" (%)	Variation between "6 months and Basal" (%)	p (value)
A (control)	19.6 ± 67.6	1.5 ± 137.3	3.5 ± 163.9	0.56131
B (experimental)	-18.1 ± 88.2	-35.1 ± 76.4	-18.9 ± 70.3	0.46962
p (value)	0.018	0.019	0.18	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

In "after irradiation and baseline" moment, while control group (A) had a change average rate of + 19.6 (indicating mean increase of 19.6% in the group ODI value), experimental group (B) had a change average rate of -18 .1 (indicating a mean decrease of 18.1% in the group ODI value) with (p = 0.018).

In "3 months and baseline" moment, control group (A) had a variation rate of + 1.5 (indicating a mean increase of 1.5% in the group ODI value) and the experimental group (B) showed a variation average rate of -35.1 (indicating a mean decrease of 35.1% in the group ODI value), with (p = 0.019).

The variation in "6 months and baseline" moment showed control group (A) with an average rate of + 3.5 (indicating a mean increase of 3.5% in the group ODI value) and the experimental group (B) with an average rate of -18.9 (indicating a mean decrease of 18.9% in the group ODI value).

6.4.2 Snoring time during sleep test recording

There was a significant difference between groups in the "After and Basal" period (p = 0.034) and between "6 Months and Basal" (p = 0.002), but there was no difference between "3 Months and Basal" (p = 0.999), as shown in the figure 43 and table 9.

Figure 43 – Snoring time rate variation of each group in the different experimental periods.
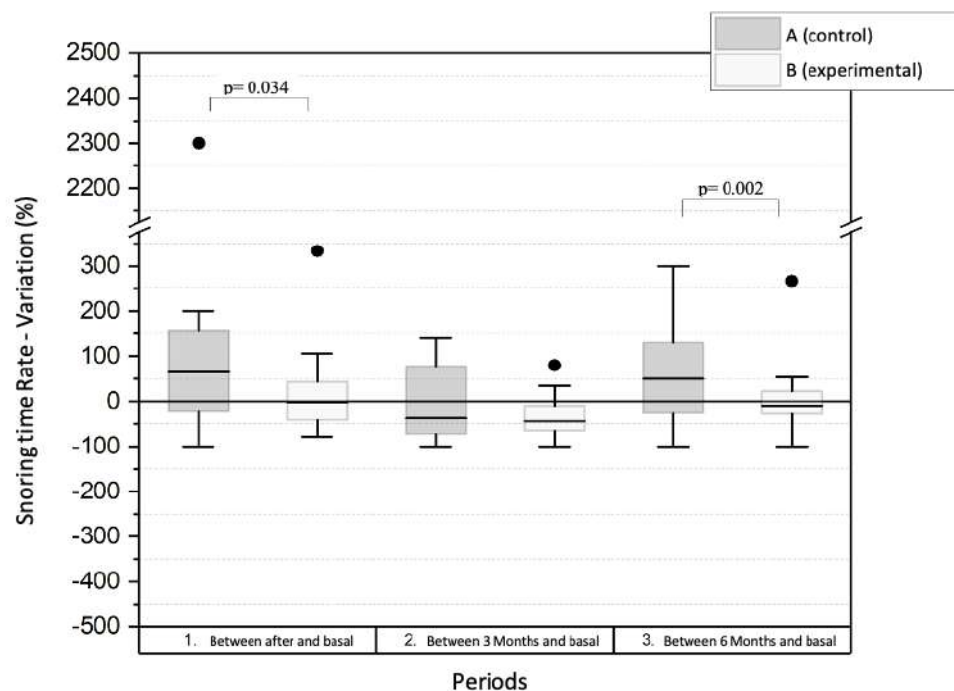
Source: personal file of the author of this dissertation.

Table 9 – Variation of Snoring Time of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variations between "3 months and Basal" (%)	Variations between "6 months and Basal" (%)	p (value)
A (control)	64.8 ± 179.1	-38.0 ± 150.1	50.0 ± 156.9	0.17377
B (experimental)	-1.5 ± 85.0	-44.6 ± 55.2	-9.1 ± 50.7	0.00225
p (value)	0.034	0.999	0.002	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

Control (A) and experimental (B) groups showed a difference in variation of snoring time rate between "after irradiation" and "baseline" and between "6 months and Basal" moments, with (p = 0.034) and (p = 0.002), respectively. While control group (A) had an average rate of change of +64.8 (indicating a mean increase of 64.8% in the group snoring time value), experiment group (B) had an average rate of change of -1.5 (indicating a mean decrease of 1.5% in the group snoring time value).

In the analysis between "3 months and baseline" moments, control group (A) had an average rate of variation of -38.0 (indicating an average decrease of 38% in the group snoring time value) and experimental group (B) showed an average rate of change of -44.6 (indicating an average decrease of 44.6% in the group snoring time value).

The variation between moments "6 months and baseline" showed control group (A) with an average rate of + 50.0 (indicating a mean increase of 50% in the group snoring time value) and the experimental group (B) with an average rate of -9.1 (indicating a mean decrease of 9.1% in the group snoring time value).

Group A did not present different snoring time when variations between the study moments were analyzed (p = 0.17377).

Group B presented present different snoring time when variations between the study moments were analyzed (p= 0.00225).

6.4.3 Snoring noise peak amplitude

There was a significant difference between the groups in the "After and Basal" period (p = 0.02984) and "6 Months and Basal" (p = 0.01472), as shown in the figure 44 and table 10.

Figure 44 – Snoring noise peak amplitude variation of each group in the different experimental periods.
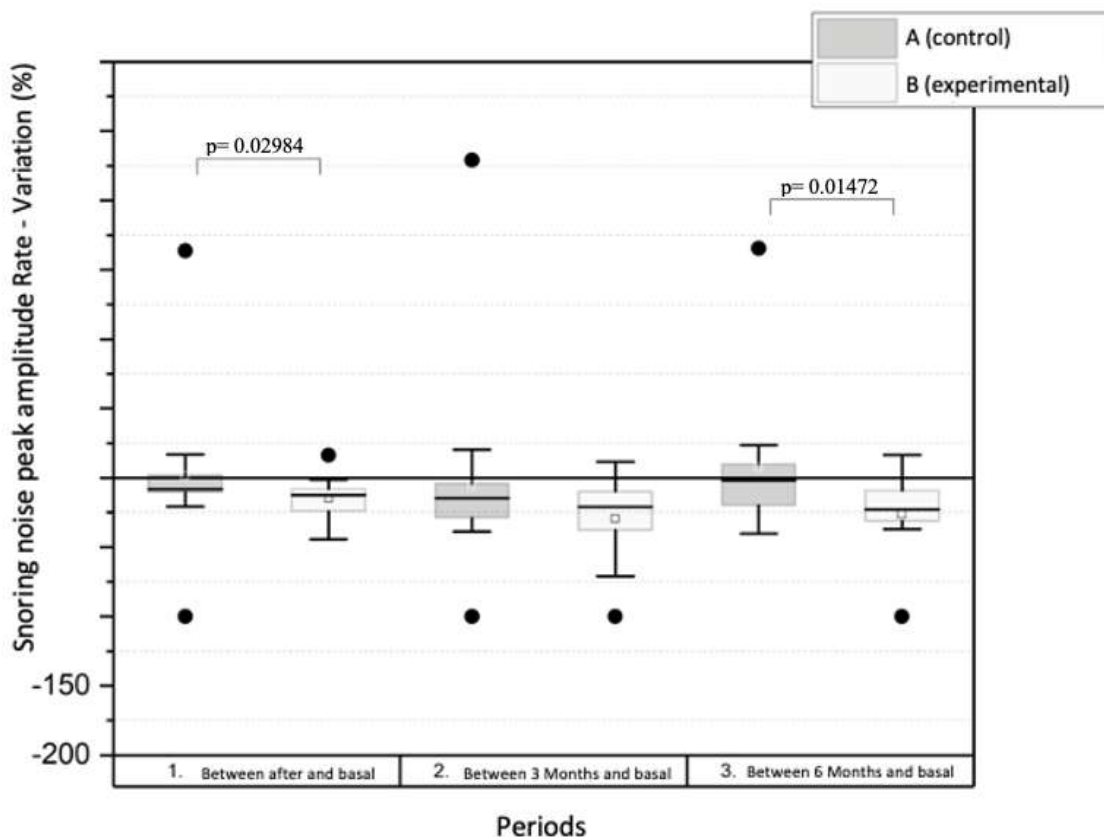
Source: personal file of the author of this dissertation.

Table 10 – Snoring noise peak amplitude variation of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variation between "3 months and Basal" (%)	Variation between "6 months and Basal" (%)	p (value)
A (control)	-8.3 ± 12.3	-14.7 ± 24.6	-2.0 ± 29.4	0.36788
B (experimental)	-12.4 ± 15.8	-21.0 ± 27.7	-22.9 ± 21.9	0.06493
P (value)	0.02984	0.37010	0.01472	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

In the period "after irradiation" and "baseline", while control group (A) had an average rate of change of -8.3 (indicating a mean decrease of 8.3% in peak amplitude of group snoring noise value), experiment group (B) showed an average rate of change of -12.4 (indicating a mean decrease of 12.4% in peak amplitude of group snoring noise value), with (p = 0.02984).

In "3 months and baseline" moment, control group (A) presented a variation average rate of -14.7 (indicating an average decrease of 14.7% in snoring noise peak amplitude value)

and experimental group (B) had a mean rate of change of -21 (indicating a mean decrease of 21% in snoring noise peak amplitude value).

The moment "6 months and baseline" showed control group (A) with an average rate of -2.0 (indicating a mean decrease of 2% in the group snoring noise peak amplitude value) and the experimental group (B) with an average rate of -22.9 (indicating a mean decrease of 22.9% in the group snoring noise peak amplitude value), with statistical difference in the variation of snoring noise peak amplitude (p = 0.01472).

6.4.4 Minimum oxyhemoglobin saturation during sleep

There was no statistical difference between the groups in any of the periods: "After and Basal" (p= 0.880), "3 Months and Basal" (p = 0.860) or "6 Months and Basal" (p = 0.296). Data are presented in figure 45 and in table 10.

Figure 45 – Variation in the minimum oxyhemoglobin saturation during sleep rate of each group in the different experimental periods.
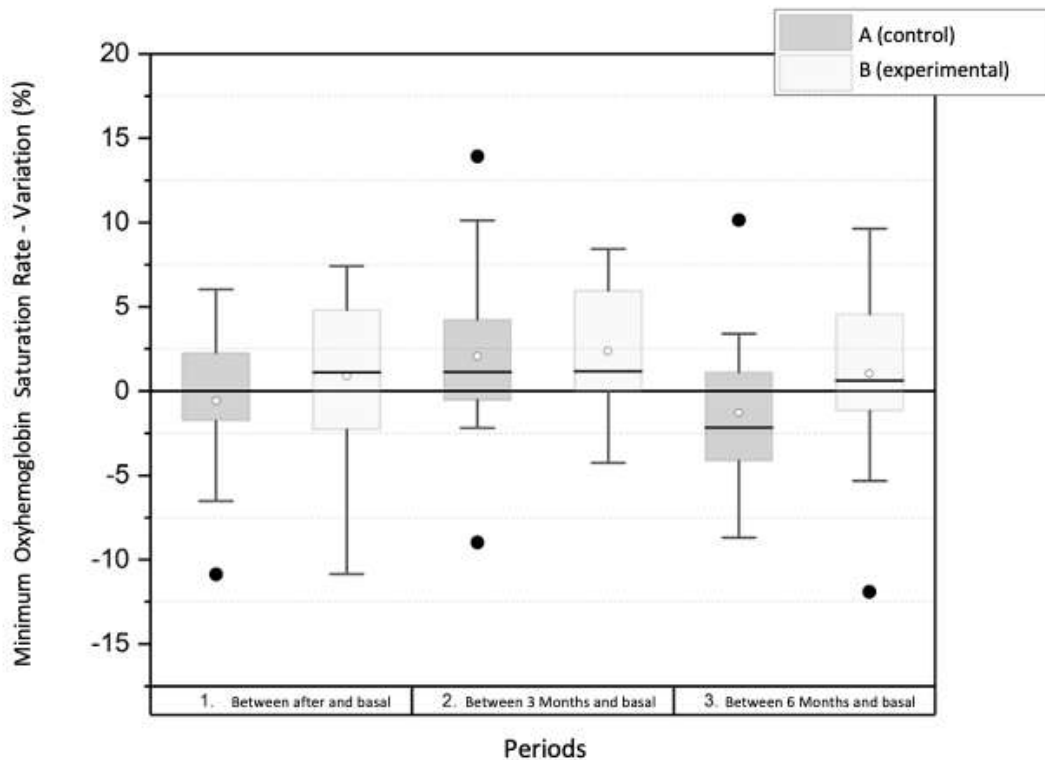
Source: personal file of the author of this dissertation.

Table 11 – Variation in the minimum oxyhemoglobin saturation during sleep rate of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variations between "3 months and Basal" (%)	Variations between "6 months and Basal" (%)	p (value)
A (control)	0.0 ± 4.0	1.1 ± 4.8	-2.2 ± 5.2	0.20255
B (experimental)	1.1 ± 7.1	1.2 ± 6.0	0.6 ± 5.7	0.57121
p (value)	0.880	0.860	0.296	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

In the "after irradiation" and "baseline" time, control group (A) had a mean rate of change of 0.0 (indicating the mean value of group minimum oxyhemoglobin saturation during sleep did not change), experiment group (B) showed an average rate of change of 1.1 (indicating a mean increase of 1.1% in the group minimum oxyhemoglobin saturation value during sleep).

In "3 months and baseline" moment, control group (A) presented a variation average rate of 1.1 (indicating an average increase of 1.1% in the group minimum oxyhemoglobin saturation value during sleep) and experimental group (B) had a mean rate of change of 1.2 (indicating a mean increase of 1.2% in the group minimum oxyhemoglobin saturation value during sleep).

The moment "6 months and baseline" showed control group (A) with an average rate of -2.2 (indicating a mean decrease of 2.2% in the group minimum oxyhemoglobin saturation value during sleep) and experimental group (B) with an average rate of 0.6 (indicating a mean increase of 0.6% in the group minimum oxyhemoglobin saturation value during sleep).

6.4.5 Average oxyhemoglobin saturation during sleep

There was no significant difference between the groups in any of the periods: "After and Basal" (p = 0.367), "3 Months and Basal" (p = 0.757) or "6 Months and Basal" (p = 0.880). Data are presented in figure 46 and in table 11.

Figure 46 – Variation in the average oxyhemoglobin saturation during sleep of each group in the different experimental periods.
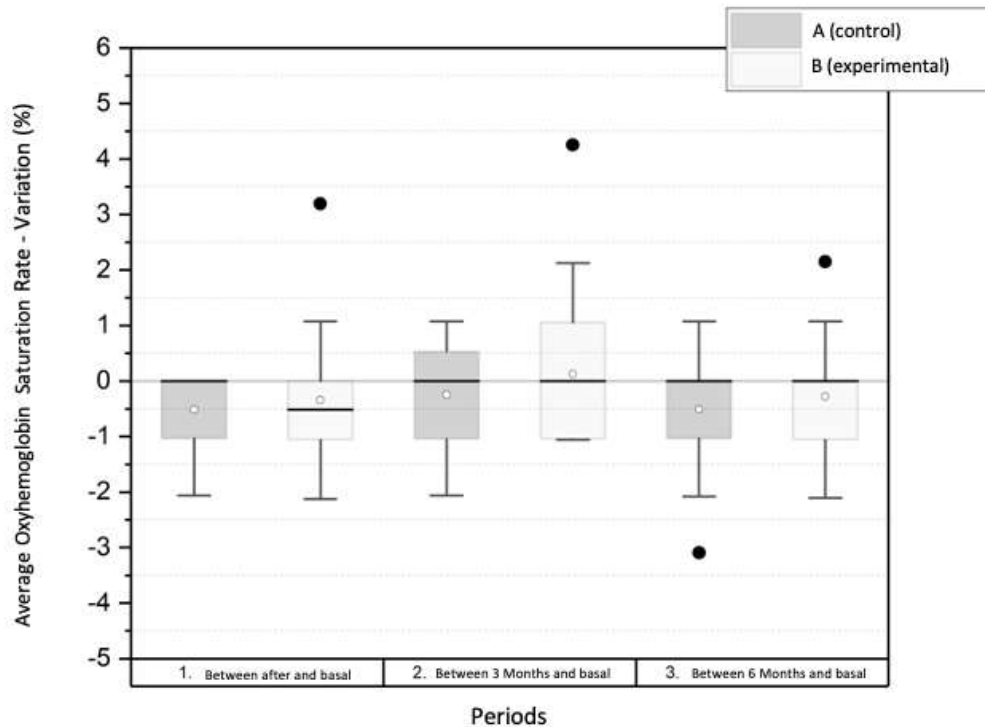
Source: personal file of the author of this dissertation.

Table 12 – Variation in the average oxyhemoglobin saturation during sleep rate of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variations between "3 months and Basal" (%)	Variations between "6 months and Basal" (%)	p (value)
A (control)	0.0 ± 1.0	0.0 ± 1.6	0.0 ± 1.0	0.77827
B (experimental)	-0.5 ± 1.1	0.0 ± 2.1	0.0 ± 1.1	0.63462
p (value)	0.367	0.757	0.880	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

Between all the comparison moments of the study, control group (A) had a mean rate of change of 0.0 (indicating the mean value of group average oxyhemoglobin saturation during sleep did not change), experiment group (B) showed an average rate of change of -0.5 (indicating a mean decrease of 0.5% in the group average oxyhemoglobin saturation value during sleep) in the "After and Basal" moment and a mean rate of change of 0.0 (indicating the mean value of group average oxyhemoglobin saturation during sleep did not change) when analysing the variation between "3 Months and Basal" and "6 Months and Basal" moments.

6.4.6 Rate of sleep time with oxyhemoglobin saturation below 90%

It was not possible to use Equation 1 to determine the variation between the analysis periods because this variable has many values equal to zero. Thus, the classification "Zero" or "Greater than Zero" was assigned to the data, making it possible to apply the chi-square test corrected by Fisher, with a significance level of $\alpha = 5\%$. There was no significant difference between the groups in any of the periods: Baseline ($p = 0.6457$), After ($p = 0.9999$), 3 Months ($p = 0.4000$) or 6 Months ($p = 0.0837$) and data are presented in figure 47 and in table 12.

Figure 47 – Variation in the sleep time with oxyhemoglobin saturation below 90% rate of each group in the different experimental periods.
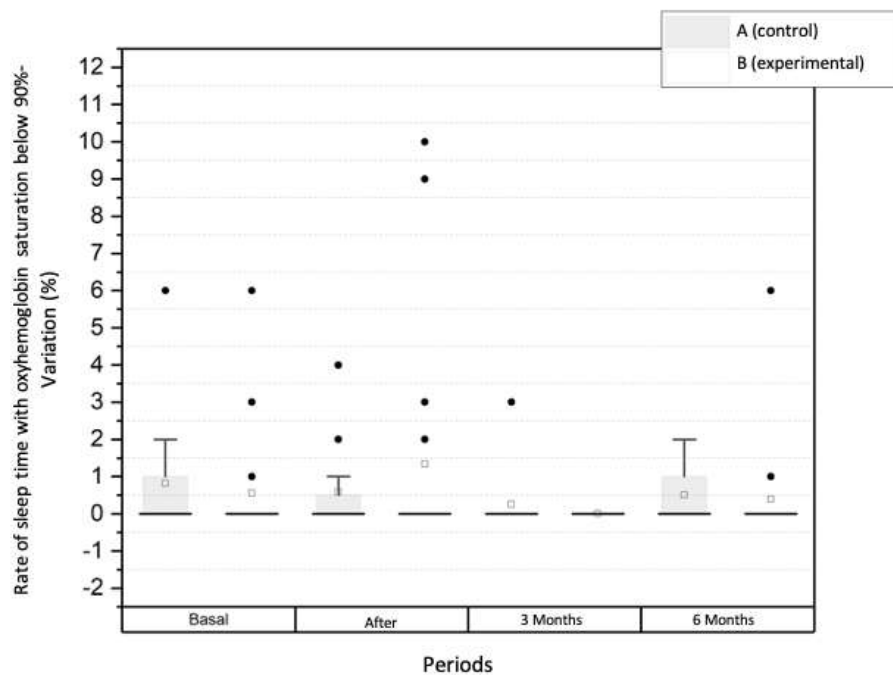
Source: personal file of the author of this dissertation.

Table 13 – Variation in rate of sleep time with oxyhemoglobin saturation below 90% of each group in the different experimental periods.

Groups	"Basal" (%)	"After" (%)	"3 months" (%)	"6 months" (%)	p (value)
A (control)	0.0 ± 1.0	0.0 ± 0.5	0.0 ± 0.0	0.0 ± 1.0	0.47092
B (experimental)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.18321
p (value)	0.6457	0.9999	0.4000	0.0837	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

Between all the moments of the study, both groups control (A) and experimental (B) had a mean rate of change of 0.0 (indicating the mean value of the groups of sleep time with oxyhemoglobin saturation below 90% did not change).

6.4.7 Rate of change in the ESE questionnaire score

The same formula (Equation 1) was used to determine the variation between the analysis periods. Then, the classification "Reduced" or "Not Reduced" was assigned to the above variation, making it possible to apply the Fisher-corrected Chi-Square test, with a significance level of α =5%.

There was significant difference between the groups in the periods "3 Months and Basal" (p = 0.00026) and "6 Months and Basal" (p = 0.00462) and data are presented in figure 48 and in table 13.

Figure 48 – Variation in ESE questionnaire score rate of each group in the different experimental periods.
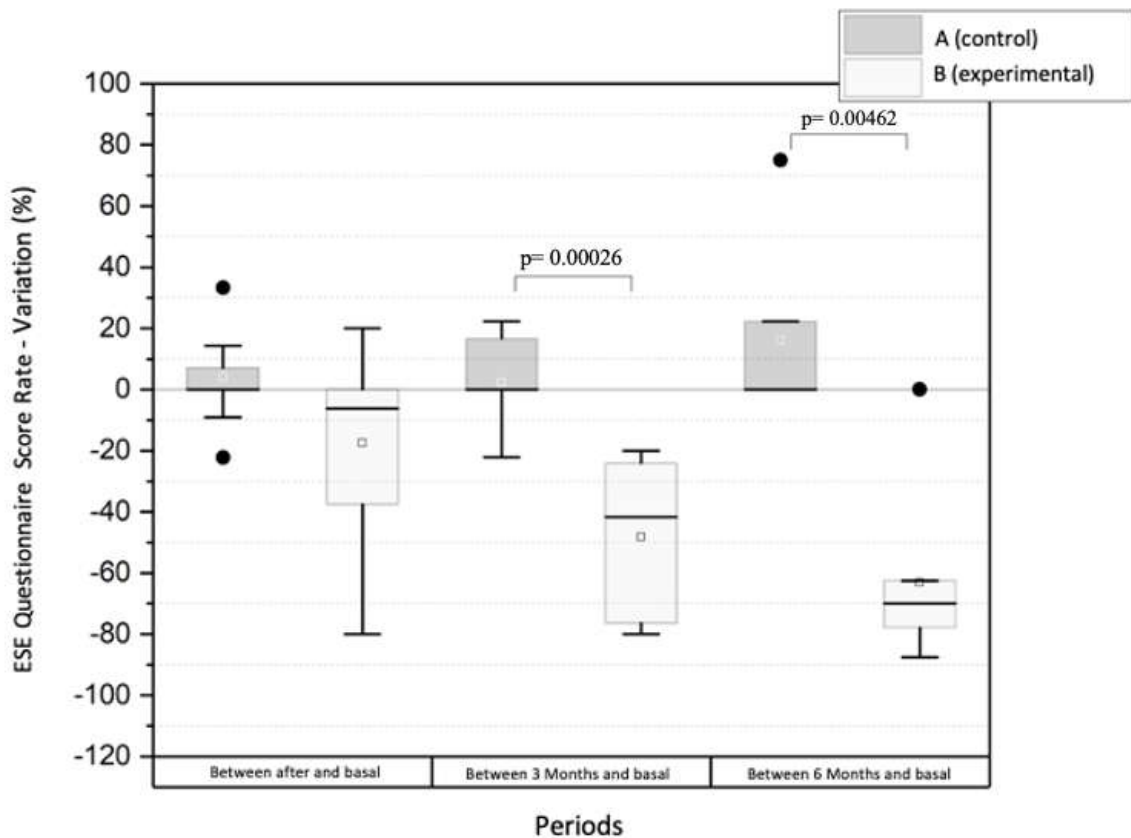
Source: personal file of the author of this dissertation.

Table 14 – Variation in the ESE questionnaire score rate of each group in the different experimental periods.

| Groups	Variation between "After and Basal" (%)	Variations between "3 months and Basal" (%)	Variations between "6 months and Basal" (%)	p (value)
A (control)	0.0 ± 7.1	0.0 ± 16.7	0.0 ± 22.2	0.88250
B (experimental)	-6.2 ± 37.5	-41.7 ± 52.4	-70.0 ± 15.3	0.01532
p (value)	0.06299	0.00026	0.00462	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

Between all the comparison moments of the study, control group (A) had a mean rate of change of 0.0 (indicating the mean value of group ESE questionnaire score rate did not change).

Experimental group (B) showed an average rate of change of -6.2 (indicating a mean decrease of 6.2% in the group ESE questionnaire score value) between the "After and Basal" moment, but with no statistical difference. But, when "3 Months and Basal" and "6 Months and Basal" moments were analyzed, there was difference (p = 0.00026 and p = 0.00462, respectively). A mean rate of change of -41.7 in "3 months and Basal" moment (indicating a mean decrease of 41.7% in the group ESE questionnaire score value) and a mean rate of change of -70.0 in "6 months and Basal" moment (indicating a mean decrease of 70.0% in the group ESE questionnaire score value), respectively.

Group A did not present difference in the ESE questionnaire score when variations between the study moments were analyzed (p = 0.88250).

Group B presented present difference in the ESE questionnaire score when variations between the study moments were analyzed (p = 0.01532).

6.4.8 Rate of change in PSQI questionnaire score

There was no significant difference between the groups in the "After and Basal" (p = 0.59699) or "6 Months and Basal" (p = 0.99999) moments , but there was statistical difference in the moment "3 Months and Basal" (p = 0.02171) and data are presented in figure 49 and in table 15.

Figure 49 – Variation in PSQI questionnaire score rate of each group in the different experimental periods.
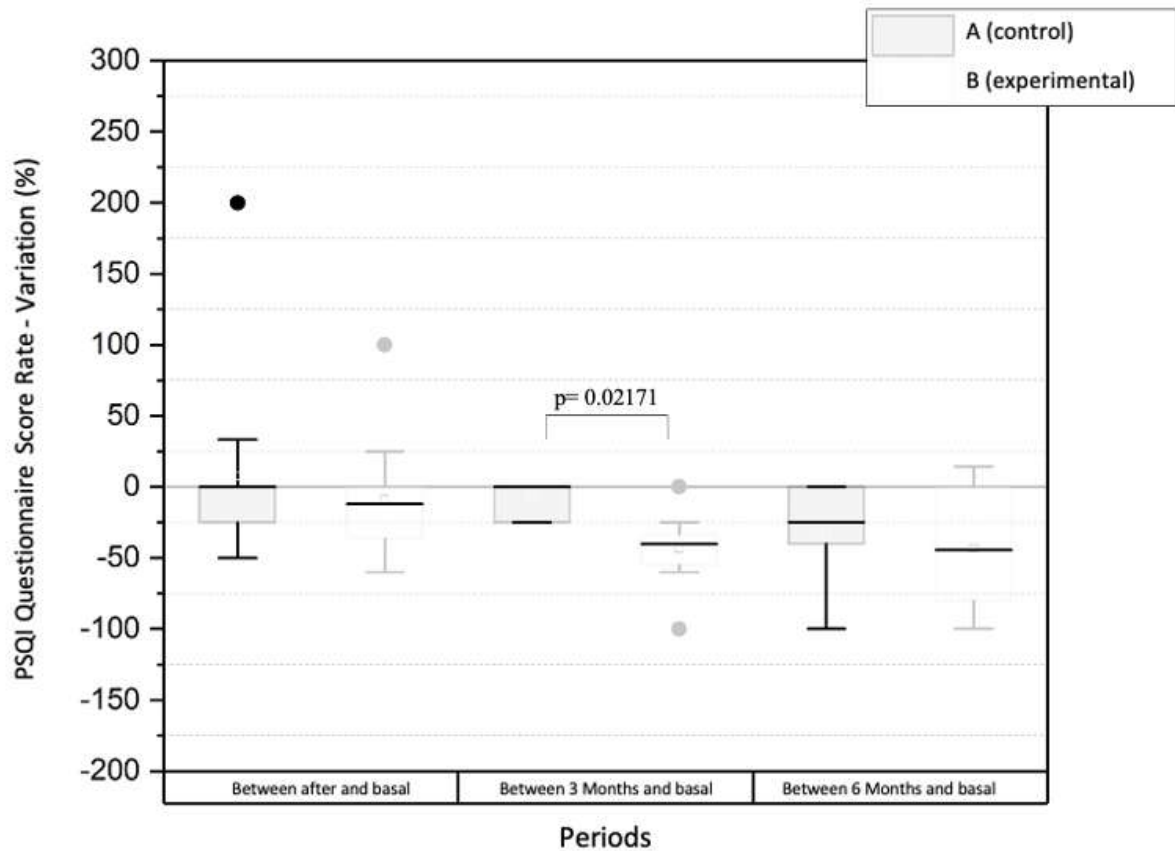
Source: personal file of the author of this dissertation.

Table 15 – Variation in the PSQI questionnaire score rate of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variations between "3 months and Basal" (%)	Variations between "6 months and Basal" (%)	p (value)
A (control)	0.0 ± 25.0	0.0 ± 25.0	-25.0 ± 40.0	0.81873
B (experimental)	-18.8 ± 36.4	-40.2 ± 21.7	-44.4 ± 80.0	0.06625
p (value)	0.59699	0.02171	0.99999	

Values represented by median ± interquartile.

In the "After and Basal" and "3 months and Basal" moments, control group (A) had a mean rate of change of 0.0 (indicating the mean value of group PSQI questionnaire score rate did not change). Between the "6 months and Basal" moments, group (A) had a mean rate of change of -25 (indicating a mean decrease of 25% in the group PSQI questionnaire score value).

Experimental group (B) showed an average rate of change of -18.8 (indicating a mean decrease of 18.8% in the group PSQI questionnaire score value) in "After and Basal" moment. In "3 Months and Basal" moment, there was a mean rate of change of 40.2

(indicating a mean decrease of 40.2% in the group PSQI questionnaire score value) and there was a difference between the groups (A) and (B) (p = 0.02171). Between "6 Months and Basal", group showed a mean rate of change of 44.4 (indicating a mean decrease of 44.4% in the group PSQI questionnaire score value).

6.4.9 Rate of change in BQ questionnaire score

There was no significant difference between the groups in "After and Basal" period (p = 0.99999) or between "6 Months and Basal" (p = 0.06993), but there was statistical difference between '3 Months and Basal" (p = 0.027).

Figure 50 – Variation in BQ questionnaire score rate of each group in the different experimental periods.
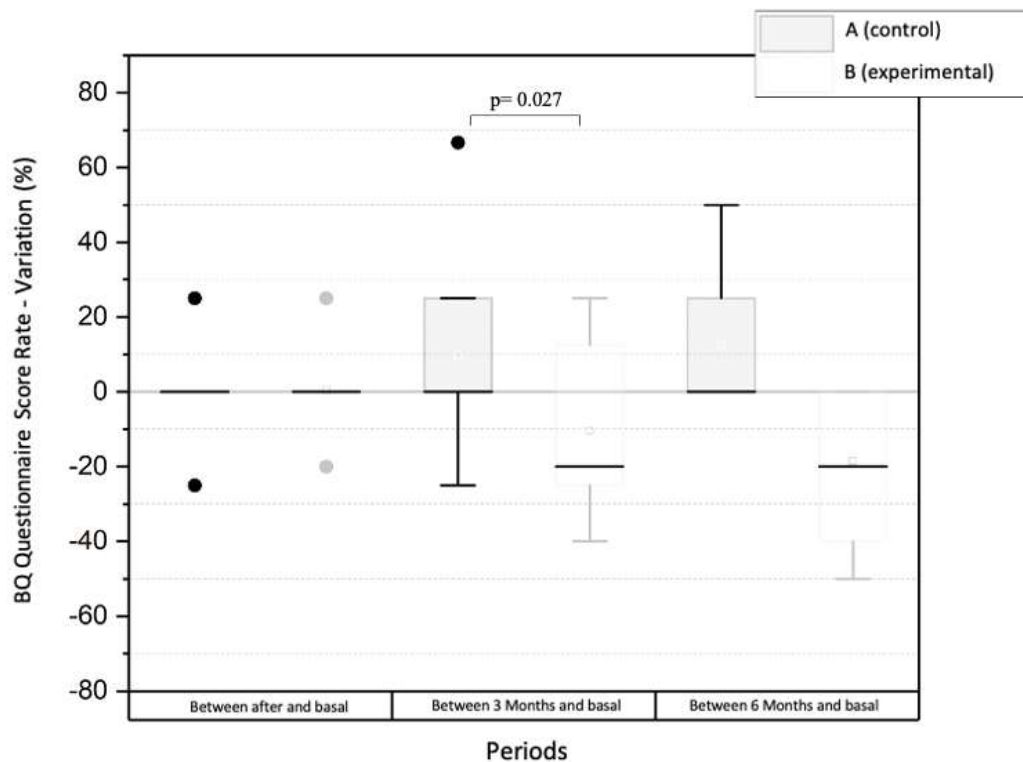
Source: personal file of the author of this dissertation.

Table 16 – Variation in the BQ questionnaire score rate of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variations between "3 months and Basal" (%)	Variations between "6 months and Basal" (%)	p (value)
A (control)	0.0 ± 0.0	0.0 ± 25.0	0.0 ± 25.0	0.68729
B (experimental)	0.0 ± 0.0	-20.0 ± 37.5	-20.0 ± 40.0	0.11320
p (value)	0.99999	0.027	0.06993	

Values represented by median ± interquartile.

Between all the comparison moments of the study, control group (A) had a mean rate of change of 0.0 (indicating the mean value of group BQ questionnaire score rate did not change), as well as the experimental group (B), at the moment "After and Basal" did.

Experimental group (B) showed an average rate of change of -20 (indicating a mean decrease of 6.2% in the group BQ questionnaire score value) in "3 Months and Basal" and "6 Months and Basal" moments, when the variation was analyzed. And there was a statistical difference between the groups (A) and (B) ($p = 0.027$) at the moment "3 Months and Basal".

7 DISCUSSION

7 DISCUSSION

7.1 About the use of lasers for SBD treatment

Clinical signs of aging, risk factor for SBD emergence and progression, such as epithelium thinning and loss of elasticity, are accompanied by structural and functional changes in extracellular matrix components, which are reduced and partially responsive. Collagen, elastin and proteoglycans respectively provide tissue tensile strength, elasticity and hydration. The amount of fibroblasts, collagen and elastic fibers decreases in aged tissue by time action or exposure to constant trauma. This reduction, combined with enzymatic degradation, leads to tissue sagging and fragility.[54,55,61,106]

A variety of methods have been used to treat obstructive sleep apnea. These include behavioral changes, use of devices and surgery, but all of them have limitations. In relation to the oropharynx soft tissues, which are flaccid due to constant trauma of snoring, making breathing difficult, in most cases, excision was indicated through surgical techniques of otorhinolaryngology. There is recurrence in most cases. These methods are invasive and require hospitalization, anesthesia, intense postoperative care, causing discomfort, swelling and withdrawal from daily activities until recovery. They often increase the risk of opportunistic infections, dysphagia, and speech difficulties. In recent years, more non-invasive techniques have been the preference of a large part of population.[37-52]

In 1994, Hollinshead referred to pharyngeal constrictor muscles as the main components of posterior and lateral walls of pharynx. It describes that superior constrictor muscle is attached posterosuperiorly to the skull base and posterior pharyngeal raphe, and anteroinferiorly to pterygomandibular raphe, mandible and lateral portion of the tongue base.[107]

In 1995, Schwab et al. evaluated UA lumen in patients with and without SBD, realizing that in all groups, the pharynx narrowest area is retropalatal. By examining this region, they observed in people without SBD, the retropalatal area is larger due to a greater lateral dimension of pharyngeal lumen, emphasizing lateral narrowing observed in patients with SBD is due to lateral walls of pharynx thickening and not skeletal changes or fat deposition in lateropharyngeal region, refuting concept that extrinsic compression of pharynx by fat layer leads to a reduction in UA in SBD.[108]

In 1997, Isono et al. concluded that the pharynx of OSA patients is structurally narrower and also more collapsible than no-OSA patients. They attribute the pharyngeal lumen reduction, not to the decrease in dilator muscles activity, but due to flaccidity in pharyngeal tube structure.[9]

Friberg et al., in a 1998 study, identified progressive neurogenic lesions signs in pharyngeal muscles caused by snoring trauma, as a possible contributing factor to upper airway collapsibility.[7]

In 2004, Sériès et al. histologically investigated the uvula of apneic and non-apneic obese snoring patients, noticing disorganization in the arrangement of elastic fibers in mucous layer of OSA patients, regardless of weight, and concluded that OSA is associated with structural tissue alterations of the UA extracellular matrix.[109]

Laser treatments to combat aging signs are quite popular nowadays. There are two basic tissue management modalities for rejuvenation: ablative and non-ablative soft tissue remodeling. Both show positive results. Non-ablative method is less invasive, brings greater comfort in post-procedure, with less infection risk, as it maintains the epithelium integrity. It emerged to avoid recurrent side effects of ablative techniques. There is evidence that the basic mechanism of action is the induction of new collagen growth due to controlled thermal tissue damage. This study shows that non-ablative remodeling with high-intensity pulsed lasers may represent a new, better-tolerated option for the treatment of this tissue, which is hampered by the constant trauma of snoring.[73,76,81-83,86 -89,106-123]

Figure 51 – Ablative and non-ablative treatment instruction.
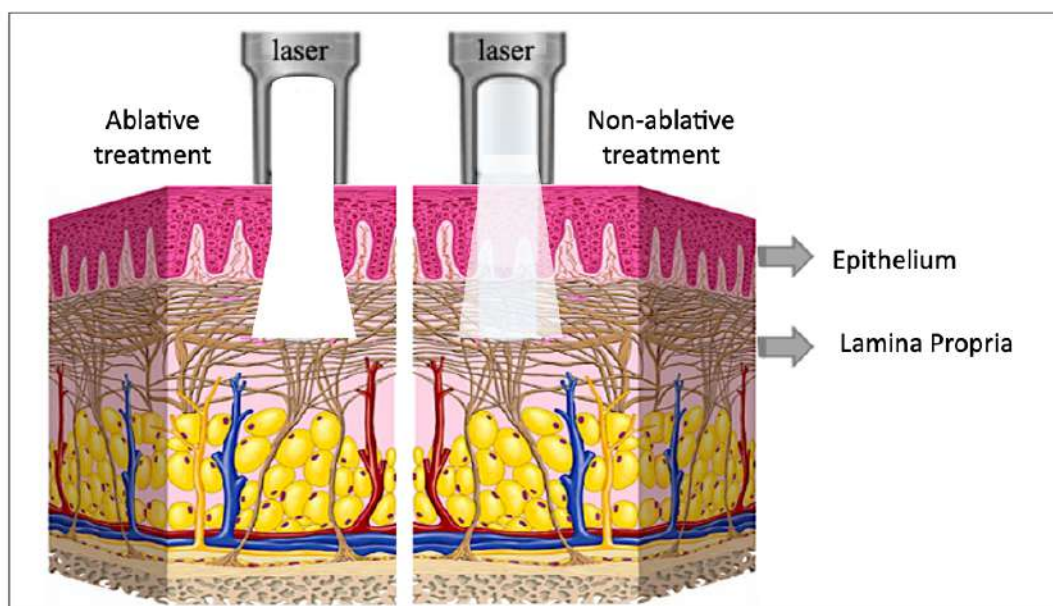
124

Use of lasers for tissue compliance treatment is based on tissue thermal damage induction, causing an acute inflammatory process. The repair process consists of replacing non-viable cells by healthy ones, with consequent tissue remodeling. The scars formation in oropharynx would bring an ability decrease to contract and relax muscles, but a paper published in 2021 by Diana Pereira and Inês Sequeira, made a comparative analysis between skin and oral mucosa, during homeostasis and wound healing, discussing the superiority of oral mucosa regenerative potential without scar formation, which positively signals the lasers indication for SBD treatment. According to the article, compared to skin, oral mucosa has an exceptional regenerative capacity, and is much less prone to scarring. There is much evidence linking excessive fibrosis seen in the skin with a strong inflammatory response to injury. Oral mucosa is the only adult tissue with the potential to heal with minimal fibrosis formation, capacity comparable only to fetal skin healing. It is known that oral mucosa fibroblasts have a migratory capacity not present in adult skin. They also have higher levels of hepatocyte growth factor expression therefore, they more effectively resist the differentiation of TGF-β1-driven myofibroblasts when compared to dermal fibroblasts. Tissue matrix metalloproteinase inhibitors show reduced activity, thus allowing an increase in MMP-2 activity in oral wound healing remodeling phase. Oral cavity submucosal layer can be compared to hypodermis in the skin, being composed of loose adipose tissue or glandular connective tissue. The repair mechanisms responsible for the superior result when compared to skin are:

- Environment: external factors such as saliva and oral microbiota. They modulate oral healing by regulating the inflammatory response.
- Inflammation: the inflammatory response is shorter and of lesser proportion.
- Angiogenesis: less inflammation in oral wounds leads to less angiogenesis, which in turn leads to less scar formation.
- Proliferation of keratinocytes: oral epithelium presents faster re-epithelialization, because keratinocytes have a greater proliferative potential and are less differentiated than skin keratinocytes, thus contributing to a greater regenerative potential.
- Fibroblasts: main actors in the healing proliferative phase, they are responsible for collagen deposition and wound contraction. In addition to the fibroblasts positive for Engrailed1 lineage subpopulation, Rinkevich and colleagues report a

population of Wnt1-positive lineage in oral mucosa, closely related to non-fibrotic healing that characterizes this mucosa.

- ECM: oral wounds show increased expression of hyaluronic acid, tenascin, fibronectin and increased ratio of collagen III to collagen I.
- Molecular signals: healthy oral mucosa is primed to respond to injury, suggesting that epithelium has a specially primed intrinsic genetic response for cell growth and proliferation in addition to the inflammatory response.[81-83,87-89,106,110]

Figure 52 – Illustration of the healing process with and without scar formation.
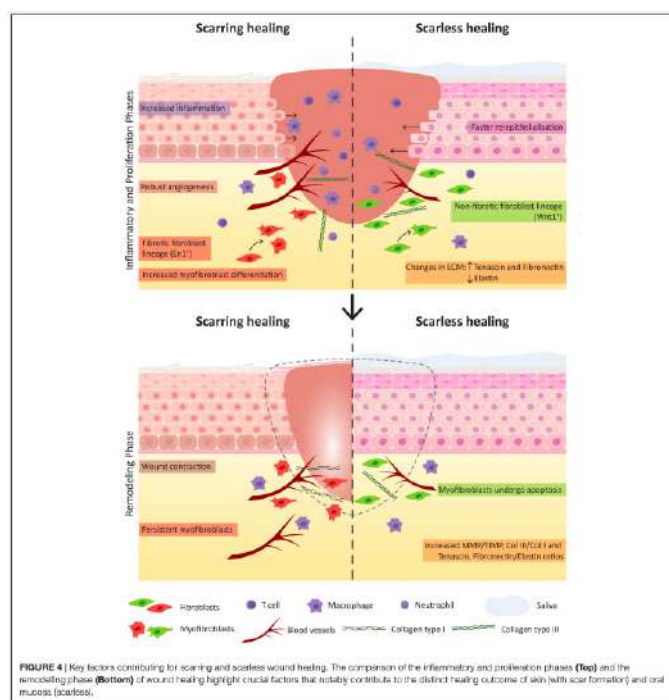
Source: Pereira D, Sequeira I. A Scarless Healing Tale: Comparing Homeostasis and Wound Healing of Oral Mucosa with Skin and Oesophagus. Front Cell Dev Biol. 2021 Jul 26;9: 682143. Doi: 10.3389/fcell.2021.682143.

7.2 About the irradiation parameters establishment

Of the articles selected for this research literature review, only one, which made combined use of two wavelengths (Er:YAG and Nd:YAG) published in 2021 related AHI improvement to the combined use of lasers. Other studies, which used only Er:YAG wavelength, showed reduction in snoring severity, without significant changes in AHI. [64-77]

Our work corroborates the 2021 study by Shiffman HS et al., confirming tissue remodeling through non-ablative combined approach of high-intensity pulsed Nd:YAG and Er:YAG lasers with subsequent improvement in oxyhemoglobin saturation parameters.[76]

After an in-depth study of laser use in sleep breathing disorder publications and clinical follow-up of professionals who already use lasers to treat snoring in their clinical practice, we defined a sequential, non-ablative five-step protocol, with the combined use of two high-intensity pulsed lasers: Nd:YAG and Er:YAG, with the aim of achieving best results with maximum safety for the patients. We used the Lightwalker AT platform, Fotona.

For a biological response to occur from interaction of laser light with living tissue, it is necessary for the radiation to be absorbed and for an effect to occur in this environment. Determining best parameters to optimize the intended response requires knowledge of biological tissue constitution and an understanding of laser light optical principles.[81,83,88,111]

Anderson and Parrish postulated that selective photothermolysis could be predicted by choosing the appropriate wavelength, pulse duration, and pulse energy for a specific target. Absorbing chromophores for the wavelength of 1064 nm (Nd:YAG) are, in descending order, melanin, hemoglobin and water. However, chromophores absorption coefficient for this wavelength is relatively low. Less absorption is balanced by greater depth of penetration. Furthermore, thermal diffusion at this optical penetration depth is reduced, which in fact makes the near-infrared region ideal for selective tissue heating.[124]

In the study published in 2011, Bashkatov et al determined absorption and reduced dispersion coefficient of human tonsillar mucosa, for the 1064 nm wavelength ($\alpha_a = 0.39$ cm^{-1}; $\alpha_{dr} = 5.2$ cm^{-1}), which allowed the Nd:YAG laser optical penetration depth estimation in human tonsillar mucosal tissue, of $L \approx 6$ mm.[111]

Figure 53 – Estimated depth of optical penetration at 1064 nm wavelength for human mucosal tissue.
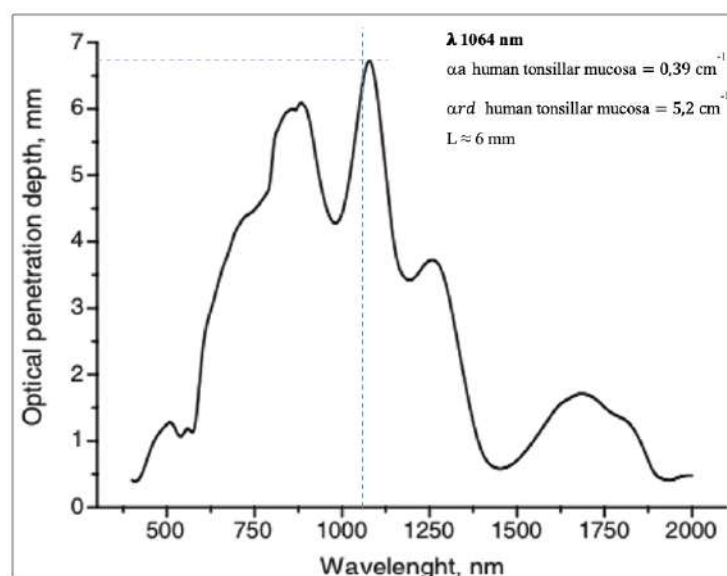
Bashkatov A, Genina E, Tuchin V. Optical properties of skin, subcutaneous, and muscle tissues: A review. Journal of Innovative Optical Health Sciences. 2011;04. Doi: 10.1142/S1793545811001319 adapted by the author of this dissertation.

According to Cho work in 2013, palatal mucosa thickness of epithelium and lamina propria vary according to their location reference to dental positioning and also according to the tooth distance. Knowing in aged tissues, epithelium is thinner and lamina propria constituent elements are present in lesser quantity, we took as a reference, the average thickness found in first molar reference region (which represents, on average, the transition between hard and soft palate). Cho also evaluated greater palatine artery estimated depth in palatal mucosa, taking positioning and distance of the teeth as reference. Thus, we assumed for this study palatal mucosal epithelium mean thickness ranged from 0.31 to 0.38 mm. And lamina propria thickness from 0.87 to 1.48 mm. Thus, mucosal layer thickness would be approximately 1.20 to 1.90 mm, and greater palatine artery would be approximately 6 mm below the epithelium surface, having maxillary first molar as reference.[98,99,100]

Figure 54 – Average thickness of epithelium and basal lamina of palatal mucosa; estimated depth of greater palatine artery in palatal mucosa.

Table 1. Epithelial thickness of the palatal mucosa according to tooth site and measurement position

Distance below the AC	CD (n=22)	P1D (n=22)	P2D (n=27)	M1D (n=30)	Overall thickness	P-value
3 mm	0.46±0.15^{ab} (0.44)	0.43±0.11^c (0.42)	0.35±0.09^a (0.35)	0.33±0.06^{bc} (0.33)	0.38±0.11	0.000*
6 mm	0.44±0.13^{def} (0.42)	0.34±0.09^d (0.36)	0.32±0.09^e (0.31)	0.30±0.06^f (0.30)	0.34±0.11	0.000*
9 mm	0.35±0.11^g (0.35)	0.32±0.08 (0.33)	0.30±0.09 (0.31)	0.28±0.05^g (0.26)	0.31±0.09	0.037*

Data (in millimeters) are mean±standard deviation (median) values. Identical letters indicate statistically significant differences among the tooth sites at the indicated measurement position (P<0.05). *Statistically significant differences among the tooth sites at the indicated measurement position (P<0.05). AC, alveolar crest; C, canine; P1, first premolar; P2, second premolar; M1, first molar; D, distal surface of the tooth.

Table 2. Lamina propria thickness of the palatal mucosa according to tooth site and measurement position

Distance below the AC	CD (n=22)	P1D (n=22)	P2D (n=27)	M1D (n=30)	Overall thickness	P-value
3 mm	1.78±0.91 (1.55)	1.31±0.50 (1.23)	1.40±0.39 (1.28)	1.47±0.53 (1.33)	1.48±0.61	0.101
6 mm	1.26±0.65^k (1.04)	1.06±0.24 (1.02)	1.04±0.31 (1.00)	0.89±0.19^k (0.85)	1.04±0.39	0.018*
9 mm	1.04±0.47 (0.92)	0.88±0.16 (0.89)	0.83±0.26 (0.78)	0.79±0.25 (0.75)	0.87±0.31	0.060

Data (in millimeters) are mean±standard deviation (median) values. Identical letter indicates statistically significant difference among the tooth sites at the indicated measurement position (P<0.05). *Statistically significant differences among the tooth sites at the indicated measurement position (P<0.05). AC, alveolar crest; C, canine; P1, first premolar; P2, second premolar; M1, first molar; D, distal surface of the tooth.

Table 3. Length and depth of the greater palatine artery (GPA) according to tooth site

	CD (n=22)	P1D (n=22)	P2D (n=27)	M1D (n=30)	Overall distance	P-value
Length	7.76±2.43^{ab}	9.21±2.55	10.93±2.17^a	11.28±1.11^b	10.25±2.29	0.003*
Depth	3.97±0.57	3.09±0.84	3.58±1.08	5.50±2.72	4.31±2.07	0.024*

Data (in millimeters) are mean±standard deviation values. Identical letters indicate statistically significant differences among the tooth sites at the indicated measurement position (P<0.05). C, canine; P1, first premolar; P2, second premolar; M1, first molar; D, distal surface of the tooth; Length, distance from the alveolar crest to the center of endothelium of the GPA; Depth, distance from the surface of the palatine mucosa to the center of endothelium of the GPA.

Cho, Kwang-Hee et al. Histological assessment of the palatal mucosa and greater palatine artery with reference to subepithelial connective tissue grafting. Anatomy & Cell Biology

Hamans EP et al in 2000 showed epithelium thickness in SBD patients is significantly greater than in controls. The study also observed the intercellular space presented conjunctive fibers distributed randomly, as a reflex of edema in submucosal region. This edema showed few connective threads, indicating that edema was actually present between the loose connective tissues, due to trauma from snoring vibration, further narrowing the pharyngeal lumen.[123]

From data that palatal mucosa has an average thickness of 1.20 to 1.90 mm and, knowing the optical penetration depth of Nd:YAG laser in human tonsillar mucosal tissue is approximately 6 mm, we have this optical penetration depth exceeds the thickness of mucosal layer, either in its normal or pathological state. Therefore, it is the submucosal tissue irradiation, allowing its thermal treatment, that leads to the improvement of analyzed parameters. The 1064 nm wavelength is mainly absorbed by oxyhemoglobin, in lamina propria blood capillaries, but also in deeper layers, with loose connective tissue and larger vessels, such as the submucosa. As, for this wavelength, scattering predominates over absorption, the photon energy, although attenuated by dispersion, is also absorbed by hemoglobin and water, at a depth that can reach up to 6 mm. This makes heat distribution more homogeneous within the tissue. [83,88,98,99,100,111,123]

Thus, we define the first and second irradiation steps parameters of our work sequence. Laser Nd:YAG (λ: 1064 nm), at 100 mm working distance, 10 mm spot diameter, energy density of 0.6 J/cm^2, temporal width of 01 millisecond at 10 Hz frequency, for deep non-ablative thermal tissue sensitization. And in a second moment, we raised the frequency to 20 Hz and kept other first step parameters. By decreasing the time interval between pulses, it was possible to increase heat treatment temperature of the irradiated region. Action mechanism is based on the release of chemical mediators by endothelial damage and subsequent activation of cell proliferation process and tissue remodeling by fibroblasts. Epithelium is preserved, which turns procedure more comfortable and at lower complications risk.[81,82,83,88,111]

Figure 55 – Parameters established for the 1st and 2nd steps of the oropharyngeal irradiation sequence.
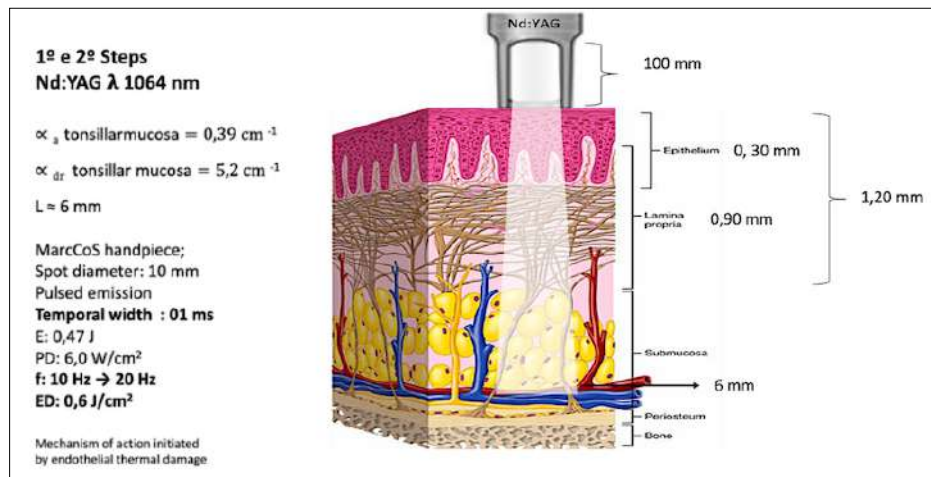
1º e 2º Steps
Nd:YAG λ 1064 nm

$\propto_a$ tonsillarmucosa = 0,39 cm^{-1}

$\propto_{dr}$ tonsillar mucosa = 5,2 cm^{-1}

L ≈ 6 mm

MarcCoS handpiece;
Spot diameter: 10 mm
Pulsed emission
Temporal width : 01 ms
E: 0,47 J
PD: 6,0 W/cm²
f: 10 Hz → 20 Hz
ED: 0,6 J/cm²

Mechanism of action initiated
by endothelial thermal damage

Nd:YAG
100 mm
Epithelium 0, 30 mm
Lamina propria 0,90 mm
1,20 mm
Submucosa
6 mm
Periosteum
Bone

Source: TEN CATE'S ORAL HISTOLOGY, page 597 – Ninth Edition. ISBN: 978-0323-48524-1/ illustration adapated for this study.

According to literature, the extremely short optical penetration depth (of a few micrometers) characteristic of Er:YAG laser in water tissue, significantly contributes to the clinically reported safety and efficacy. Temperature rise is not limited to a specific pigment, but to the entire superficially irradiated tissue layer (thickness defined by laser optical penetration depth) and subsequent thermal diffusion. Ablation occurs if the maximum tissue temperature during a laser pulse reaches the ablation temperature. Conceptually, ablation results from micro-explosions of superheated water contained in an elastic tissue (water confined within tissue cannot expand freely.Thus, the ablation temperature is higher than water boiling temperature under atmospheric pressure – Tabl ≈ 250º C). For fluences below the ablation threshold, tissue maximum temperature increases approximately linearly with fluence. Maximum temperature increases with laser fluence until ablation threshold fluence is reached. At this point, maximum tissue temperature reaches the ablation temperature. For fluences above ablation fluence, maximum temperature remains fixed at the ablation temperature, similar to the case of boiling water that maintains its temperature at 100º C regardless of heating power.[61,70,74,81-89,117,118]

Figure 56 and 57 – Dependency relationship between tissue surface temperature and laser pulse fluency; Dependency relationship between ablation depth and laser pulse fluence.
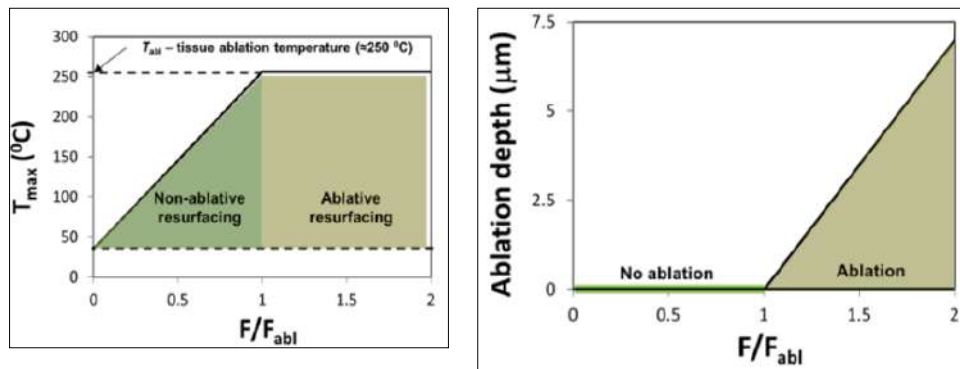
Lukac M, Gaspar A, Bajd F. Dual Tissue Regeneration: Non-Ablative Resurfacing of soft Tissues with FotonaSmooth® Mode Err:YAG Laser.

Non-ablative Er:YAG laser treatment uses thermal approach to induce only epithelial and connective tissue remodeling, without evident epithelial damage. The action mechanism is based on causing thermal damage to tissue, resulting in a reactive inflammatory response, with a biosynthetic capacity increase of fibroblasts and other cells, inducing an optimal physiological environment reconstruction, cellular activity enhancement, hydration, synthesis of collagen and elastin.[88,89,112,116,119-122]

Figure 58 – Non-ablative tissue remodeling with Er:YAG laser.
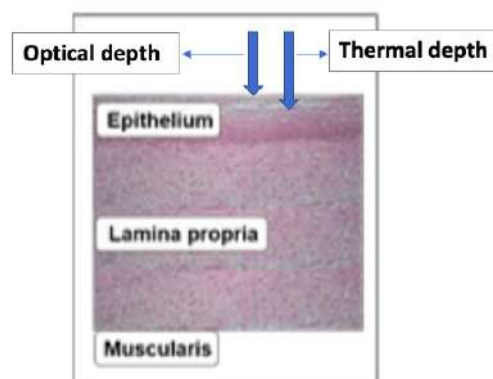
Lukac M, Gaspar A, Bajd F. Dual Tissue Regeneration: Non-Ablative Resurfacing of Soft Tissues with FotonaSmooth® Mode Er:YAG Laser adapted by the author of this dissertation.

During and after optical pulse, heating produced in target can be conducted to its surroundings, heating adjacent tissue depending on irradiated pulse duration. Irradiation times shorter than target thermal relaxation time allow the heat produced to remain confined to target. Irradiation times longer than thermal relaxation time allow the heat diffusion to adjacent tissues, with damage to surrounding structures possibility. [81-83,86-89]

Figure 59 – Duration and temporal shape of optical and thermal pulses; cooling phase duration of thermal pulses at different depths of optical penetration.
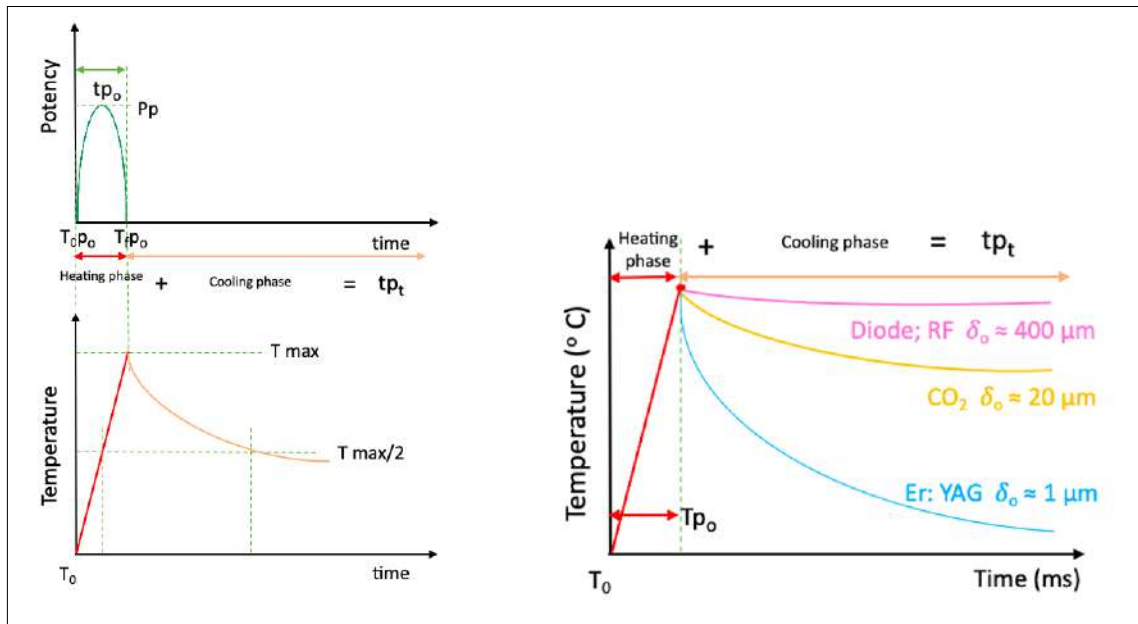
Third step parameters of our work irradiation sequence were established using Er:YAG Laser (λ: 2940 nm), at 20 mm of working distance, 7 mm of spot diameter, energy density of 2 J/cm², temporal width of 06 milliseconds at 10 Hz frequency. The handpiece has pixel screen optical technology, which allows diffusion of heat both in depth and radially, allowing energy delivery at a temperature below the tissue ablation threshold, under the irradiation conditions described here.

Due to high absorption of Er:YAG laser photons by tissue water, the optical penetration depth is extremely short, which allows excellent thermal diffusion. Temperature rise takes place in the irradiated tissue surface layer (thickness determined by laser optical penetration depth) and subsequent thermal diffusion. Thermal response depth is determined by the amount of heat that can be delivered to tissue non-ablatively. Therefore, use of long pulses is a popular approach. However, coagulation depths beyond 30-50 μm are not possible with Er:YAG single-pulse exposure, but are effective in inducing tissue regeneration process because they activate production of cytokines that moderate inflammatory process by thermal injury directly in keratinocytes, stimulating healing by increasing cell proliferation in basal layer of oral mucosa epithelium. By paracrine signaling, fibroblasts are activated for synthesis

of collagen, elastin and decrease in expression of some metalloproteinases, in addition to proliferation, differentiation and migration of fibroblasts to epithelium, in response to damage.[81,83,88,89,116,117,119]

Figure 60 – Parameters established for the 3rd step of the oropharyngeal irradiation sequence.
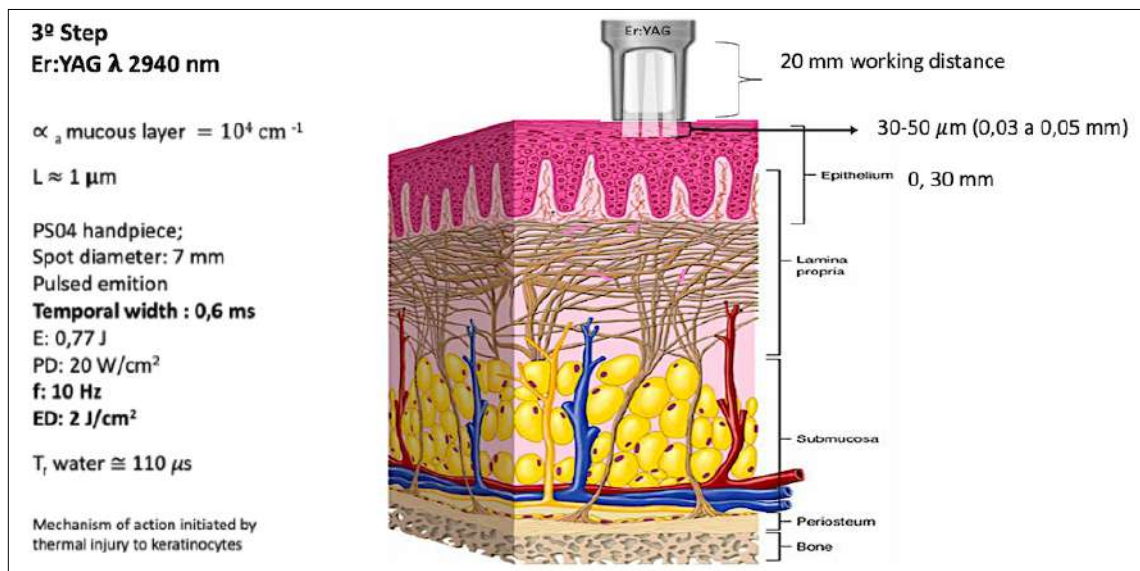
Source: TEN CATE'S ORAL HISTOLOGY, page 597 – Ninth Edition. ISBN: 978-0323-48524-1/ illustration adapated for this study.

Low optical penetration depth of 2940 nm wavelength, which is a few micrometers, favors heated tissue cooling, due to high temperature gradient with the surface. This enables controlled energy delivery without tissue ablation. Parameters must allow the thermal pulse to have a longer duration than tissue thermal relaxation time, such temperature does not reach the critical threshold for ablation. Thus, for pulsed emission lasers, pulse width, repetition rate and energy density are the parameters that define whether a procedure will be ablative or not.[81,83,88,89,117,119]

Fourth and fifth steps followed in order to deliver energy with gradually heat production in irradiated tissues. In fourth step, with Er:YAG laser (λ 2940 nm) now in pulse-train mode, with temporal width of 300 milliseconds, repetition rate of 1.5 Hz and energy density of 5.0 J/cm². And fifth step, with the same wavelength and temporal width, repetition rate of 2.0 Hz and energy density of 9.0 J/cm².

In non-ablative procedures, longer the duration of laser pulse, greater the depth of thermal diffusion. It is not optical penetration depth, but the heat penetration depth, which determines the heat-affected tissue depth. With extremely long pulse, operating without tissue ablation to decrease compliance, the formation of collagen and elastin is stimulated by

damage to epithelium surface and also to tissue deeper layers (lamina propria reticular layer), by activating the inflammatory response by fibroblasts, with collagen and elastin synthesis.[89,116,117,119]

Figure 61 – Parameters established for 4th and 5th steps of the oropharyngeal irradiation sequence.
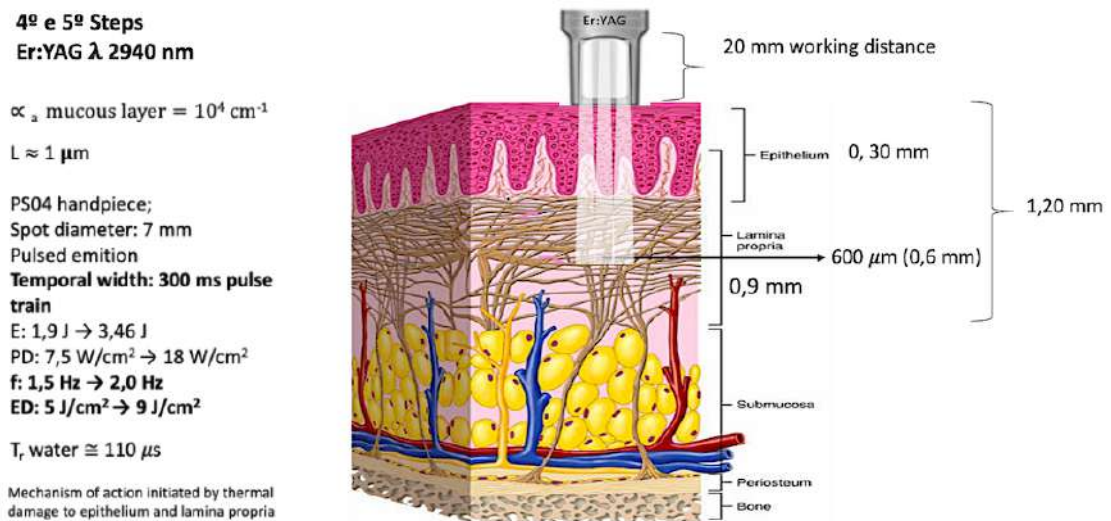
Source: TEN CATE'S ORAL HISTOLOGY, page 597 – Ninth Edition. ISBN: 978-0323-48524-1/ illustration adapated for this study.

The pulse train mode, patented as FotonaSmooth, consists of delivering Er:YAG laser energy in a sequence of six sub ablative micropulses delivered consecutively within the 300 millisecond macropulse, thus allowing the irradiation time to be longer than water thermal relaxation time. The micropulse sequence "pumps" heat generated by laser onto tissue surface, by diffusing heat away from the surface to a depth of up to 600 microns, allowing heat treatment of the lamina propria deepest layer.[89,112,116,117,119]

Figure 62 – Sequence of micropulses with subsequent thermal diffusion; depth of optical penetration and thermal penetration.

Figure 63 – The temperature evolution in "Fotona Smooth" pulse train mode with production of two different temperature peaks and different regenerative processes triggered.
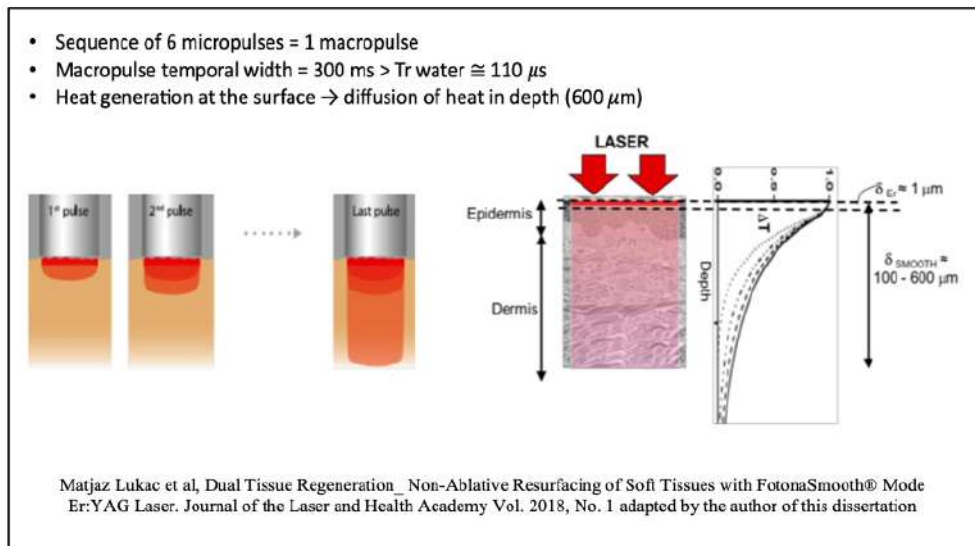
Temperature evolution in pulse train mode is distinguished by the production of two different temperature peaks:

1) "fast" temperature peaks, indicated on figure 63 graph as "Tp2i", which characterize the individual short pulses; and

2) "slow" temperature peak, indicated on figure 63 graph as "Tp1", defining the long-term thermal "pulse"maximum temperature, produced in baseline.

And it produces thermal damage with different characteristics. The very short, initial high-temperature pulses generated at epithelium surface by Smooth mode of the highly absorbed Er:YAG laser are transformed through heat diffusion into a long-lasting thermal pulse within deeper connective tissue. As a result, there are two complementary regenerative processes initiated by the same treatment: an indirect triggering effect by epithelium short-term thermal pulse and a direct and slow thermal injury to lamina propria connective tissues.[89,112,116,119,120]

Source: Matjaz Lukac et al, Dual Tissue Regeneration_ Non-Ablative Resurfacing of Soft Tissues with FotonaSmooth Mode Er:YAG Laser. Jornal of the Laser and Health Academy, vol. 2018, No 1 adapted forthis study.

At the top and left in figure 63, FotonaSmooth macropulse, consisting of six micropulses, and in lower portion, temperature evolution on epithelium surface during a Smooth pulse, over time. Laser parameters are set to provide peak micropulse temperatures and peak macropulse temperatures below their respective critical temperatures for excessive tissue injury. The short temperature spikes amplitude is not critical for patient comfort or safety. For short duration thermal pulses (< 1 ms), critical temperature for tissue damage is above the tissue ablation threshold of about 250° C, thus preventing reaching the critical level for tissue damage.[89,112,116,119,120]

Dual process of tissue remodeling, in figure 63 on the right, is possible because Smooth mode use allows the ability to generate very intense heat pulses of very short duration (< 1 ms) on epithelium surface (within ≈ 1 μm), involving biochemical process of short exposure and subsequent triggering of deeper tissues regeneration, in addition to heating by the slower thermal pulse, in deeper tissues (between ≈ 100 μm and 600 μm), with relatively slower regeneration, involving long-exposure biochemical process, by Er:YAG laser, in the same treatment. Superficial thermal injury, produced by high temperature rapid spikes, leads to heat shock proteins (HSP) production, which promotes a temporary modification in cellular metabolism and a possible controlled generation of reactive oxygen species (ROS), which would stimulate healing by increasing in keratinocytes and fibroblasts proliferation , that

would lead to production of collagen and extracellular matrix, thus enhancing the tissue remodeling process, complementary to conventional direct slow stimulation of fibroblasts, resulting from thermal injury caused by the slow temperature peak.[89,112,116,119-121]

Figure 64 – Synergistic effect on tissue remodeling by the association of Nd:YAG and Er:YAG lasers.
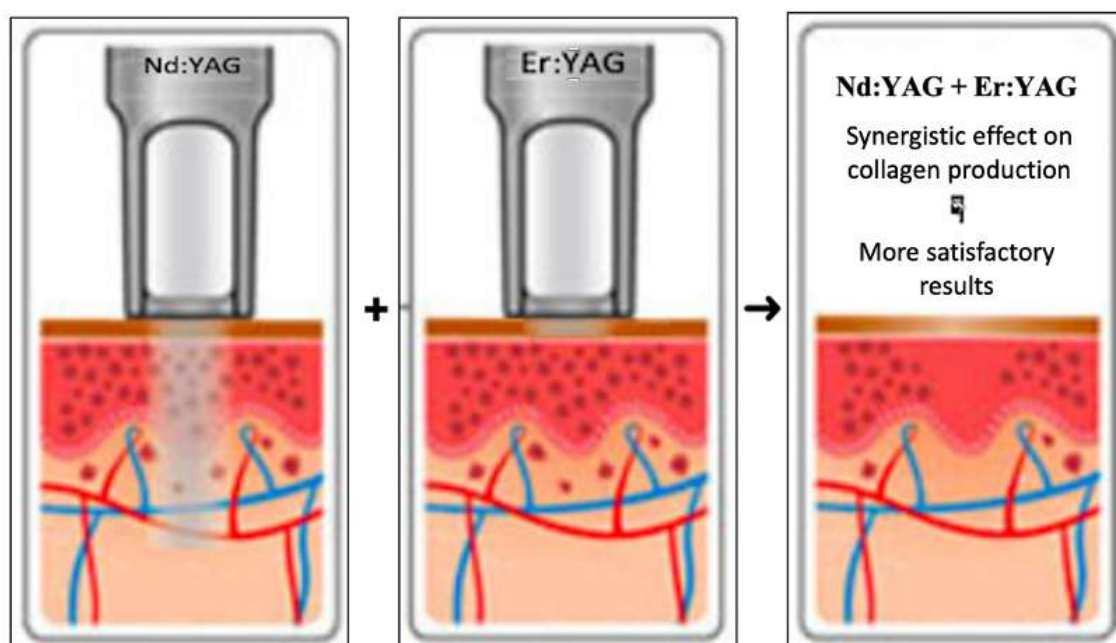
Source: web image modified by the author of this dissertation.

The advantage of this sequential non-ablative protocol with combined use of two high-intensity pulsed lasers, Nd:YAG and Er:YAG compared to other more deeply penetrating energy sources such as CO_2, diode or radiofrequency (RF) lasers, is due to the greater tissue heat treatment depth without ablation and action of different regenerative mechanisms, ensuring patient safety and treatment efficacy.[112]

By combining two wavelengths (Er:YAG and Nd:YAG), allowing thermal sensitization of epithelium, lamina propria and submucosa, the tissue remodeling process with decreased compliance was initiated by direct signaling from both keratinocytes and fibroblasts. There was reestablishment of tonic and phasic physiological capacity, that is, tissue recovered its ability to control an imbalance reflexively and unconsciously; and to perform movement, consciously and voluntarily, producing more satisfactory results for maintenance of pharyngeal patency during sleep, which resulted in improvement of the observed health parameters. Non-ablative action mechanism is based on controlled and selective tissue thermal damage, causing an inflammatory response, which results in the increase in regenerative capacity of the remaining viable cells, inducing reconstruction of

optimal physiological environment, tissue hydration, synthesis of collagen and elastin, essential for tissue compliance treatment resulting from advancing age or from constant trauma such as snoring.[89,119]

7.3 About the main outcome: UA lumen enlargement due to decreased tissue compliance

Sleep breathing disorder has a major economic impact on healthcare systems worldwide. It is important to be aware the noise produced during sleep can represent a health problem, with high risk of morbidity and mortality. The gold standard therapy, using continuous positive air pressure (CPAP) is effective, but non-adherence to treatment often occurs. Other therapeutic options also have limitations. Since treatment aims at reestablishing the upper airways patency, allowing airflow passage for breathing during sleep, the approach that expands the oropharyngeal space through the high-intensity pulsed lasers use, in a non-invasive way, seems to be promising. This study had very homogeneous groups at baseline, in modified Mallampati classification, age, sex and BMI ($p = 0.80096$, $p = 0.56370$; $p = 0.76509$; $p = 0.99999$, respectively) . And this made it possible to show very clearly that laser treatment modifies the oropharynx space for passage of breath and the result is still perceptible six months after the end of treatment, as shown by comparison of modified Mallampati classification records at the end of treatment and at return for 3 and 6 months follow-up with baseline. The difference between groups after irradiation and at three and six months follow-up was statistically significant ($p = 0.00258$, $p = 0.00641$ and $p = 0.01432$, respectively) and agreement between the four evaluators (principal researcher and three independent evaluators, blinded and calibrated for the study) was a determining point to guarantee reliability of the study result, with ICC ranging from 0.84 to 0.93 for single measurements and from 0.96 to 0.98 for average measurements ($p < 0.001$).

7.4 About secondary outcomes

With the increase in the UA lumen due to the decrease in tissue compliance, the respiratory flow during sleep was restored and other parameters also were analyzed to verify if the treatment response showed a statistically observed difference.

As the intervention proposed in our study still lacks robust evidence of effectiveness for treatment of SBD, our main objective was to observe the behavior of the group that

received treatment and compare it to the group that did not receive it, recording perceived differences at different times of the study thus creating subsidies to indicate the proposition therapeutic or not.

The percentage variation of each analyzed parameter was calculated. Then, the classification "Reduced" or "Not Reduced" was attributed to the above variation, allowing the statistical analysis of the recorded difference (Fisher corrected chi-square test, with significance α =5%).

7.4.1 Decreased ODI and outcome comparison with other approaches reported in literature

Table 17 – ODI rate variation of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variation between "3 months and Basal" (%)	Variation between "6 months and Basal" (%)	p (value)
A (control)	19.6 ± 67.6	1.5 ± 137.3	3.5 ± 163.9	0.56131
B (experimental)	-18.1 ± 88.2	-35.1 ± 76.4	-18.9 ± 70.3	0.46962
p (value)	0.018	0.019	0.18	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

According table 7, there was difference between the groups when the variation rate between the "After and Baseline" (p = 0.018) and "3 months and baseline" (p = 0.019) was verified.

It was also possible to observe that group A (control) showed positive variation at all times of the study, indicating a mean increase in the group ODI value, while experimental group (B) had a mean decrease in the group ODI value, throughout the study, showing the difference in the behavior of the groups.

The literature points to the reduction in the absolute value of the oxygen desaturation index (ODI) parameter as the main indicator of success of proposed treatments for SBD.

With the intention of establishing a comparison with other publications, we also statistically analyzed the raw data from our study. The results of this analysis are found in detail in the appendix of this dissertation.

In a study published in 2021, the main SBD treatments were listed, as well as the success rate of each therapy (defined as treatment capable of reducing AHI by at least 50% or, to a value of less than 5 events per hour), in addition to the main limitations of each approach. CPAP therapy presented a 59.3% success rate, intraoral device for mandibular advancement,

68%, uvulopalatopharyngoplasty (UPPP), which promotes the compliant upper airways tissue excision, presented a 44.35% success rate, according to Xia F publication.[51]

Our work used type IV polysomnography as outcome measure and, therefore, we found ODI values. But, according to the American Academy of Sleep Medicine, a minimum drop of 3% to 4% in oxyhemoglobin saturation is a criterion for defining hypopnea. Thus, Apnea and Hypopnea Index (AHI) and Oxyhemoglobin Desaturation Index (ODI), used to grade AHI severity, are strongly correlated in accuracy, sensitivity and specificity, fact confirmed in a study published in 2020.[29,30]

At the end of the treatment, 66.67% of the patients in the experimental group showed less than five events per hour or reduction equal or greater than 50% of the ODI, results comparable to other approaches used to treat SRD.[51]

Puhan and colleagues conducted a randomized controlled trial in 2006 and concluded that playing didgeridoo for 4 months had a positive effect on daytime sleepiness, snoring, and AHI.[49]

Ieto V and colleagues in a study conducted in 2015, which included patients with snoring and OSA, showed myofunctional speech therapy exercises improve snoring, indicating effectiveness of the therapeutic proposal, but found no statistically significant difference in AHI improvement. The study also presented a table summarizing profile of patients in the treated group and AHI results before and after speech therapy treatment from three other publications in addition to results of the work they conducted.[50]

As AHI and ODI are strongly correlated, it points to the possibility of comparing results obtained in our study with those presented in the table by Ieto et al., since they all aim at restoring UA patency by treating compliance without tissue excision in SBD patients.

Table 18 – Profile of patients who participated in studies with therapeutic proposition to restore UA patency during sleep, by decreasing tissue compliance and without tissue exeresis, for patients with SBD.

variables	Puhan et al. (2005)	Guimarães et al. (2009)	Diaferia et al. (2013)	Ieto et al. (2015)	This study (2022)
Treated N/Total N	14/25	16/31	27/100	14/39	18/30
Age	49.9 ± 6.7	51.5 ± 6.8	45.3 ± 13.0	48.1 ± 13.6	48.0 ± 9.0
BMI (kg/m²)	25.8 ± 4.0	29.6 ± 3.8	25.0 ± 7.4	28.1 ± 2.7	28.0 ± 7.3
SBD severity	only moderate AOS	only moderate AOS	No information	PS, mild AOS, moderate AOS	PS, mild AOS, moderate AOS
AHI or ODI basal (events/hour)	22.3 ± 5.0 ↓48%	22.4 ± 4.8 ↓39%	28.0 ± 22.7 ↓50,4%	15.6 ± 9.3 ↓15%	9.2 ± 8.2 ↓52,2%
AHI or ODI after intervention	11.6 ± 8.1	13.7 ± 8.5	13.9 ± 18.5	13.4 ± 7.4	4.4 ± 4.3
p (value)	$= 0.05$	< 0.01	< 0.001	$= 0.127$	$=0.209$

BMI: body mass index; AHI: apnea and hypopnea index; ODI: oxyhemoglobin desaturation index; PR: primary snoring; OSA: obstructive sleep apnea. Values represented by median ± interquartile range. The probability that the detected difference occurred by chance is the value represented by p.

Although the benefits brought by speech therapy exercises to patients with snoring and OSA are undeniable, there is a need to practice daily in order to obtain positive results. And long-term adherence to the daily practice of exercises is still a challenge in SBD patients treatment. The observance of reduction in ODI mean values six months after the end of treatment positively signals the treatment approach with association of Nd:YAG and Er:YAG lasers for SBD. Patients attend three treatment sessions, with an average duration of 20 minutes every 14 days. The results of reduced compliance with muscle tone reestablishment for upper airway patency during sleep and reduction in ODI values are still perceptible after six months.

As for the results, our study got an average 52% reduction in ODI value and success of therapy can be defined as a treatment capable of reducing AHI/ODI by at least 50%.

Ieto et al study reported a median reduction of 25% in AHI value in the treatment of patients with moderate OSA. Our study also observed an important improvement in the group with greater severity of SBD. We obtained a 48% reduction in ODI mean value of patients with moderate OSA at the end of treatment. At three-months follow-up after irradiation, the mean reduction in ODI reached 75%. And six months after the end of treatment, these patients still had a 56% mean reduction in the ODI value. Our work also found a reduction in the mean value of ODI in patients with mild OSA. At the end of the treatment, we obtained a 35.5% mean reduction in ODI value. Three months after the end of treatment, we still found a mean reduction of 34% in the ODI value of these patients and at the 6-month follow-up, ODI mean value was still 11.6% lower. We did not observe reduction in ODI mean value of patients with an initial ODI of less than five events per hour.[50]

In a study published in 2021, Shiffman and colleagues reported a mean reduction of 66.3% in the ODI of patients treated with the combination of Nd:YAG and Er:YAG lasers. It was not reported whether the result was maintained after treatment.[76]

Our study did not include critically ill patients. And, we work with a Nd:YAG laser protocol less aggressive, since thermal diffusion properties for palatal mucosa at 1064 nm are very reduced when compared to the Er:YAG laser, and even so, we obtained excellent results at the end of treatment, with improvement observed in returns for follow-up at 3 and 6 months.

In order to establish a comparison between Shiffman studies in 2021 and ours in 2022, we present a comparison with the main points of interest in both studies:

Comparison between the findings of the Shiffman study in 2021 and our work in 2022

variables	Shiffman (2021)	This study (2022)
Treated-N/ Total-N	27/27	18/30
Control group use	no	yes
Study design	Retrospective study - case series	Controlled, randomized, double-blind clinical trial
Age (years)	53 (25 -78)	48 (31 − 65)
Gender	20 men; 9 women	9 men; 9 women
BMI (kg/m^2)	20,5 < BMI< 39 (information obtained from 63% of patients)	28
SBD Severity	IAH > 5	PS, mild OSA, moderate OSA
IAH or basal ODI (events/hour)	6 < IAH < 60	9,2 ± 8,2
IAH or ODI after intervention (events/hour)	-	4,4 ± 4,3
P (value)		0,209
Decrease in IAH/ODI	66,3%	52,2%
Nd: YAG	P: 10 W; DE: 40 J/cm^2 (spot 2mm used blurred to produce an 8mm dot on fabric); pulse width: 25ms; repetition rate: 8Hz	DE; 0,6 J/cm^2 (spot 10 mm); pulse width: 1 ms; repetition rate: 10 Hz and in a second moment: 20 Hz
Er: YAG	P: 4–5,15 W; DE: 7–9 J/cm^2 (spot 7 mm); pulse width: 300 ms; repetition rate: 1,5 Hz	DE: 2 J/cm^2 (spot 7 mm); pulse width: 0,6 ms; repetition rate: 10 Hz DE: 5 J/cm^2 (spot 7 mm); pulse width: 300 ms; repetition rate: 1,5 Hz DE: 9 J/cm^2 (spot 7 mm); pulse width: 300 ms; repetition rate: 2,0 Hz

BMI: body mass index; AHI: apnea-hypopnea index; IDO: oxyhemoglobin desaturation index; PR: primary snoring; OSA: obstructive sleep apnea. Values from our study, represented by the median and its respective interquartile range. The probability that the detected difference occurred by chance is the value represented by p.

7.4.2 Decreased severity of snoring

Table 19 – Variation of Snoring Time of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variations between "3 months and Basal" (%)	Variations between "6 months and Basal" (%)	p (value)
A (control)	64.8 ± 179.1	-38.0 ± 150.1	50.0 ± 156.9	0.17377
B (experimental)	-1.5 ± 85.0	-44.6 ± 55.2	-9.1 ± 50.7	0.00225
p (value)	0.034	0.999	0.002	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

Analyzing the control group (A) it is evident the great variability of behavior between nights regarding the time of sleep with snoring, despite the patients of both groups having performed the polysomnography exams using a positional band for lateral decubitus, at all times during the study. Even so, there was a significant difference between groups in "After and Basal" period (p = 0.034) and between "6 Months and Basal" (p = 0.002).

Control (A) group showed a mean increase of 64.8% in the group snoring time value after treatment, a decrease of 38% after 3 months and a mean increase of 50% in the group snoring time value after 6 months.

Experimental group (B) presented decrease in the group snoring time value in all moments of the study.

Table 20 – Snoring noise peak amplitude variation of each group in the different experimental periods.

Groups	Variation between "After and Basal" (%)	Variation between "3 months and Basal" (%)	Variation between "6 months and Basal" (%)	p (value)
A (control)	-8.3 ± 12.3	-14.7 ± 24.6	-2.0 ± 29.4	0.36788
B (experimental)	-12.4 ± 15.8	-21.0 ± 27.7	-22.9 ± 21.9	0.06493
P (value)	0.02984	0.37010	0.01472	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.

There was a significant difference between the groups in the "After and Basal" period (p = 0.02984) and "6 Months and Basal" (p = 0.01472), and the percentage reduction in the peak amplitude of snoring noise was more pronounced in the experimental group at all times of the study, as shown in table 9.

Although the excellent results of decrease in snoring time during recording of sleep exam and snoring noise peak amplitude in the experimental group, it is worth noting that snoring noise plays an important role as clinical sign of SBD. As a treatment outcome evaluation parameter, it should be observed with parsimony, given that a patient after being treated, may have a longer snoring time during the night sleep. And this is due to the pathophysiology of the disease and not to the therapeutic approach applied.

As for snoring noise peak amplitude, it is valid as an objective measure of result, allowing to quantify the difference observed in different moments of the study. However, many patients showed a significant decrease in snoring noise during sleep, with a small difference in peak amplitude, which occurred in a short time and very sporadically.

7.4.3 About minimum and average oxyhemoglobin saturation and sleep time with saturation below 90%

Although there was no statistically perceptible difference in minimum and average oxyhemoglobin saturation and in sleep time with saturation below 90%, the results show the experiment group presented a superior response to the control group in these three parameters: Sleep time with saturation below 90%:

At baseline, 16.67% of the experimental group had saturation below 90% during sleep. At the end of treatment, this number rose to 22%. At the 3-month return, 0% of the sample showed saturation below 90% and at the 6-month return, this number represented 11.11% of the group.

Average saturation:

At the end of treatment, 22% of the experimental group showed an improvement in the mean oxyhemoglobin saturation value. At the 3-month and 6-month follow-up, this number was 27% and 16.67% of the group, respectively.

Minimum saturation:

At the end of the treatment, 50% of the experimental group showed improvement in the minimum oxyhemoglobin saturation. At the 3-months and 6-months follow-up, this number was 72.22% and 50% of the group, respectively.

7.4.4 About the self-reported data:

Patient perception of a particular therapeutic approach outcome is a fundamental factor in long-term adherence to treatment. Thus, self-reportd data were also part of this study outcome measures, with Epworth, Pittsburgh and Berlin questionnaires, which respectively assess daytime sleepiness, sleep quality and snoring perception. At the end of irradiation, clinical improvement was slight for most patients, although some of them already perceived it more clearly, according to the questionnaires scores. On return for 3-months follow-up however, the improvement perception gained relevance, evidencing that improvement is perceived gradually.

A statistical difference in the ESE score, that assesses daytime sleepiness, was noted in 3 and 6 months follow up. Although it was not noticed after treatment, control group had no change at that moment and the experiment group showed a 6.2 reduction in the score, showing difference in result pattern. A similar situation was seen in the PSQI score, about sleep quality, at the end of treatment and at the 6-month follow-up (with no change in control group and experiment group showing a reduction in score to 18.8 and 44.4, respectively). At the 3 months follow-up moment, it was statistically different. Finally, the same in the BQ score, which assesses the perception of snoring severity, with statistically perceived difference at 3-month return and showing superiority in comparison with the control group, at 6 months follow-up (no change in control group against 20.0 reduction in group experimental score).

7.5 About effectiveness of the therapeutic approach

We could certainly observe the clinical improvement of patients whose region of upper airways greatest constriction corresponded to oropharynx. To our knowledge, the result might not be positive if obstruction was in nasopharynx or hypopharynx. Another point to note is tissue compliance represents just one of the SBD risk factors. There are other points to consider, given the complexity, chronicity and multifactorial nature of this disease, which highlights the importance of multidisciplinary approach for the patients treatment. And precisely for this reason, our study analyzed the percentage variability of each parameter over time, comparing the behavior of control and experimental groups at different times of the study, finding out if patients actually responded positively to the proposed therapy or not.

Table 21 – Variation rate of all variables analized in this clinical trial, in the different experimental moments.

VARIATION RATE IN THE DIFFERENT EXPERIMENTAL MOMENTS (%)		
	CONTROL (n=12)	EXPERIMENTAL (n=18)	
	Median ± interquartile range	Median ± interquartile range	P (value)
Modified Mallampati Index *			
After and Baseline	0.0 ± 0.0	-25.0 ± 50.0	0.00060 *
3 Months and Baseline	0.0 ± 0.0	-25.0 ± 50.0	0.00159 *
6 Months and Baseline	0.0 ± 0.0	-12.5 ± 50.0	0.00403 *
Oxyhemoglobin Desaturation Index (ODI) *			
After and Baseline	19.6 ± 67.6	-18.1 ± 88.2	0.018 *
3 Months and Baseline	1.5 ± 137.3	-35.1 ± 76.4	0.019 *
6 Months and Baseline	3.5 ± 163.9	-18.9 ± 70.3	0.180
Snoring Time *			
After and Baseline	64.8 ± 179,1	-1.5 ± 85.0	0.034 *
3 Months and Baseline	-38.0 ± 150.1	-44.6 ± 55.2	0.999
6 Months and Baseline	50.0 ± 156.9	-9.1 ± 50.7	0.002 *
Snoring Noise Peak Amplitude *			
After and Baseline	-8.3 ± 12.3	-12.4 ± 15.8	0.02984 *
3 Months and Baseline	-14.7 ± 24.6	-21.0 ± 27.7	0.37010
6 Months and Baseline	-2.0 ± 29.4	-22.9 ± 21.9	0.01472 *
Minimum Oxyhemoglobin Saturation			
After and Baseline	0.0 ± 4.0	1.1 ± 7.1	0.880
3 Months and Baseline	1.1 ± 4.8	1.2 ± 6.0	0.860
6 Months and Baseline	-2.2 ± 5.2	0.6 ± 5.7	0.296
Average Oxyhemoglobin Saturation			
After and Baseline	0.0 ± 1.0	-0.5 ± 1.1	0.367
3 Months and Baseline	0.0 ± 1.6	0.0 ± 2.1	0.757
6 Months and Baseline	0.0 ± 1.0	0.0 ± 1.1	0.880
Oxyhemoglobin Saturation Below 90%			
Baseline	0.0 ± 1.0	0.0 ± 0.0	0.6457
After	0.0 ± 0.5	0.0 ± 0.0	0.9999
3 Months	0.0 ± 0.0	0.0 ± 0.0	0.4000
6 Months	0.0 ± 1.0	0.0 ± 0.0	0.0837
ESE Questionnaire Score *			
After and Baseline	0.0 ± 7.1	-6.2 ± 37.5	0.06299
3 Months and Baseline	0.0 ± 16.7	-41.7 ± 52.4	0.00026 *
6 Months and Baseline	0.0 ± 22.2	-70.0 ± 15.3	0.00462 *
PSQI Questionnaire Score *			
After and Baseline	0.0 ± 25.0	-18.8 ± 36.4	0.59699
3 Months and Baseline	0.0 ± 25.0	-40.2 ± 21.7	0.02171 *
6 Months and Baseline	-25.0 ± 40.0	-44.4 ± 80.0	0.99999
BQ Questionnaire Score *			
After and Baseline	0.0 ± 0.0	0.0 ± 0.0	0.99999
3 Months and Baseline	0.0 ± 25.0	-20.0 ± 37.5	0.02700 *
6 Months and Baseline	0.0 ± 25.0	-20.0 ± 40.0	0.06993

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p. The graphic sign of * indicates there was a statistically perceptible difference in the analysis of the results.

Evaluating all aspects measured in this study, as shown in table 17, from patient perspective, such as snoring reduction/resolution, improvement in sleep quality and daytime sleepiness, in addition to objectively observed respiratory parameters, by polysomnography and in photographic records, by comparing UA lumen with the modified Mallampati index, this treatment approach seems to be very promising for sleep breathing disorder. There was no need for hospitalization, anesthesia or medication. There were also no complications or adverse effects, such as pain, bleeding, infection, dysphagia or speech alteration, and consequent withdrawal from daily activities, observed in the surgical approach postoperative period. And the differences were statistically significant in seven of the ten parameters analyzed in the study.

The same perception of superiority in the results of the experiment group was observed with the objective data, for the moments in which the difference was not statistically noticed. ODI in 6 months return showed a 3.5 events per hour increase in control group, while experimental group presented a 18.9 events per hour decrease. Decrease in sleep time with snoring and in the snoring noise peak amplitude in 3-months follow up was also more pronounced in the experiment group (44.6% – 38.0% and 21% – 14.7%)

The clinical results of our work show that tissue remodeling is a gradual process, which increases proportionally with the number of treatments, with elapsed time and that can be maintained for up to 6 months after thermal tissue stimulation. Further studies are needed to assess the results longevity and therapy effects for longer periods than the 6 months reported in this study and may produce evidence to recommend this approach, either as a first-line treatment or as a combination therapy, integrating SBD management guidelines.

In addition, the reestablishment of tissue tonic and phasic physiological capacity, with very satisfactory results in maintaining pharyngeal patency during sleep, positively signals this therapeutic approach is also interesting in dysphagia management, another clinical condition related to pharynx tissue compliance, enabling patient to take care of their health. And not all other therapeutic approaches would bring this benefit. Surgeries for tissue excision in the SBD treatment, for example, can worsen dysphagia.

The health market scenario points to a strong tendency to manage operational costs in assistance. With the increase in life expectancy, effective preventive actions to control highly prevalent chronic diseases, such as arterial hypertension and type II diabetes, resulting from the worsening and progression of SDB, which can be carried out in a few outpatient visits, would certainly represent savings important to healthcare organizations around the world.

The association of the use of lasers in the management of patients with sleep-disordered breathing can bring great benefit to society, to the patient quality of life, to the

management of health costs, in addition to contributing to the process of permanent education in the team. multidisciplinary.

8 CONCLUSION

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Sleep dentistry plays an important role in the treatment of the patient, being able to act both in the craniofacial structure, through AIO_{AM}, posturally modifying the position of the mandible, and in histological alterations of the oropharynx, through the treatment of tissue compliance with the use of pulsed lasers of high intensity shown in this work.

The expected outcome was achieved as we were able to clearly answer the research question.

Yes, in the working conditions described in this study, the non-ablative treatment of SDB with high-intensity pulsed Nd:YAG and Er:YAG lasers expands the UA lumen, facilitating the passage of air during breathing. The procedure is performed on an outpatient basis, without the need for medication or anesthesia. The patient returns to daily activities immediately after the treatment, without any type of restriction. The treatment result leads to improved sleep quality, snoring disorder and daytime sleepiness analyzed. And it contributes to the improvement of the health parameters observed through the exams performed.

9 SUPPORT

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10 PERSPECTIVES

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As the next step in this work, we thought of expanding the number of services and segmenting the work groups according to the severity of the SBD, working in partnership with other research centers. It would be of great importance to evaluate the association between the therapeutic approach of this study and the use of intraoral appliances for mandibular advancement, as we would thus have the expansion of the lumen due to the decrease in compliance of the soft tissues in the oropharynx region and also due to the change in the positioning of the bone bases during sleep, acting more effectively in the treatment of these patients.

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12 ANNEXES

Anexo 1- Aprovação da pesquisa pelo CEP FOUSP

USP – FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE DE SÃO PAULO – FOUSP

DADOS DA EMENDA

PARECER CONSUBSTANCIADO DO CEP

Título da Pesquisa: Avaliação clínica do uso de laser de Er:YAG no distúrbio do ronco
Pesquisador: Denise Maria Zezell
Área Temática:
Versão: 4

CAAE: 44068621.8.0000.0075
Instituição Proponente: Faculdade de Odontologia da Universidade de São Paulo
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.019.423

Apresentação do Projeto:

As informações aqui apresentadas foram retiradas do documento PB_INFORMAÇÕES_BÁSICAS_1831
500_E1.pdf de 27 de setembro de 2021."Este estudo será um ensaio clínico controlado, randomizado e duplamente cego, com o objetivo de eliminar possíveis fontes de viés. Os participantes são esclarecidos que serão distribuídos de forma aleatória entre grupos de trabalho e que existe a possibilidade de serem incluídos no

grupo controle, que não recebe tratamento. Se ficar comprovada de forma positiva a utilização do laser para tratamento do ronco, os pacientes do grupo controle poderão receber o tratamento que apresentar o melhor resultado clínico.Serão incluídos no estudo, quarenta e cinco participantes com diagnóstico médico de ronco primário, apneia obstrutiva do sono leve ou moderadaque já tenham iniciado tratamento com uso de dispositivo de avanço mandibular, CPAP ou não, e que atendam aos critérios de inclusão e exclusão para esta pesquisa.

Para inclusão dos participantes nesta pesquisa, consideramos como participantes não tratados para o ronco e apneia, todos aqueles que aoreceberem o diagnóstico médico indicativo de sua condição de saúde bem como as opções terapêuticas para o tratamento e quedecidiram de formaconsciente a não aderir às mesmas ou ainda, as abandonaram por conta própria, depois de alguma tentativa sem êxito. Para os participantes que já tiverem iniciado o tratamento, não será necessária a interrupção ou suspenção deste já iniciado.

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USP – FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE DE SÃO PAULO – FOUSP

Continuação do Parecer: 5.019.423

Caso o tratamento com laser se mostre positivo,existe a possibilidade de que a terapia inicial necessite de um ajuste. Para os casos de uso do aparelho intraoral deavanço mandibular, talvez sejanecessário titular o dispositivo para diminuir o avanço, protegendo assim a articulação temporomandibular do paciente. Para aqueles que fazem uso de Cpap, talvez seja necessária a diminuição da pressão de ar, o que ofereceria maior conforto respiratório ao paciente. O pesquisador responsávelse compromete a informar e orientar o participante caso isso seja necessário." "O participante da pesquisa comparece à clínica do Laboratório Especial de Laser em Odontologia da FOUSP, em 1 pré-atendimento, 3 sessões deatendimento com uso de laser, de 20 a 30 minutos e 3 sessões de acompanhamento de 3, 6 e 12 meses após tratamento. No pré-atendimento, seleção para participação: indivíduos que se adequam aos critérios de inclusão do estudo, explicação detalhada sobre a pesquisa e se aceite livrede convite, assinam TCLE. Avaliação de percepção do ronco, sonolência e qualidade do sono por questionários. Medidas de circunferência dopescoço, cintura e IMC. Na casa do paciente, o ronco é medido e gravado durante o sono. O índice de dessaturação de oxigênio é registrado, por smartphone, oximetria de alta resolução e software específico cedidos a ele, nessa ocasião, para esse fim. Estes parâmetros e imagens defotografia do interior de boca feitas antes e após o uso do laser, servirão de base para comparação com os dados de igual teor obtidos na consulta de acompanhamento, 3 meses após o último atendimento com laser."

Objetivo da Pesquisa:

As informações aqui apresentadas foram retiradas do documento PB_INFORMAÇÕES_BÁSICAS _1831500_E1.pdf de 27 de setembro de 2021. "Objetivo Primário: Avaliar clinicamente o efeito de um tratamento não ablativo com laser de Érbio no distúrbio de ronco e no volume das vias aéreas superiores dapopulação brasileira.

Objetivo Secundário: Analisar subjetivamente a percepção da eficácia da intervenção com laser de Érbio no tratamento do ronco pelos participantes da pesquisa, pormeio da aplicação de questionários abordando a queixa do ronco, sonolência diurna e qualidade do sono, comparando osresultados antes e depoisda intervenção.Análise visual comparativa das vias aéreas (índice de Mallampati modificado) da população estudada, levando em consideração a faixa etária, o gênero, o IMC, medidas de circunferência do pescoço, padrão oclusal, consumo de

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SAO PAULO

Página 02 de 05

USP – FACULDADE DE ODONTOLOGIA DA UNIVERSIDADE DE SÃO PAULO – FOUSP

Continuação do Parecer: 5.019.423

Medicamentos e presença de apneia, antes eapós o tratamento com laser proposto para o ronco; Avaliar e comparar o índice de dessaturação de oxigênio e a saturação da oxi-hemoglobinamínima durante o sono, bem como o tempo em que a saturação permaneceu abaixo de 90%, de cada participante, no início e final dotratamento;Avaliar o impacto do tratamento do ronco com laser na amplitude do ruído e no tempo de registro de ronco durante o sono, comparandoos registros antes e depois do tratamento."

Avaliação dos Riscos e Benefícios:

As informações aqui apresentadas foram retiradas dos documentos PB_INFORMAÇÕES_BÁSICAS_ 1831500_E1.pdf e TCLE_Plataforma_Brasil_modificado_em_setembro_para_emenda.docx de 27 de setembro de 2021. "Riscos:

Consideramos que o presente estudo pode trazer como risco para o participante da pesquisa, a terapia não ter o efeito desejado ou ter efeitotransitório. Como desconforto, pode ocorrer a sensação de incômodo local, por sensação de calor leve, na região que recebe a luz. O pesquisadorresponsável se compromete a suspender a pesquisa imediatamente ao perceber qualquer desconforto aoparticipante da pesquisa, decorrente do estudo. O pesquisador e a instituição assumem a responsabilidade de dar assistência integral a qualquer complicação e danos que por ventura possam ocorrer.

Benefícios: O estudo avalia se o uso do laser de érbio pode trazer benefícios no tratamento do ronco e o participante da pesquisa tem a possibilidade de ter agravidade de seu ronco diminuída ou eliminada, melhorando a qualidade do sono. Se os resultados forem positivos, no futuro,essa terapia com laser de érbio pode representar uma nova abordagem para o tratamento do ronco, contribuindo assim para a redução de doenças crônicas e uso de medicamentos, além de contribuir com a melhora da qualidade do sono e consequentemente, da qualidade de vida das pessoas."

Comentários e Considerações sobre a Pesquisa:

Este estudo será um ensaio clínico controlado, randomizado e duplamente cego (participante e avaliador), que incluirá 45 participantes com diagnóstico médico de ronco, apneia obstrutiva leve ou moderada. Serão utilizadas três intervenções: placebo, laser Er:YAG não ablativo equipamento Fotona (após pré-tratamento com ND:YAG), laser Er:YAG não ablativo Lifetouch. Os desfechos

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Continuação do Parecer: 5.019.423

Serão avaliados e comparados antes e 3, 6 e 12 meses após a intervençãoe incluem a avaliação subjetiva por meio de questionários validados sobre qualidade do sono, bem comomedidas objetivas de intensidade do ronco e registros de polissonografia tipo IV, incluindo oxigenação dosangue e frequência cardíaca, além das medidas pelo índice de Mallampati medidas por fotografias do interior de boca.

A presente EMENDA (E1) compreende a mudança do local onde o paciente deverá receber a aplicação do laser com o equipamento Lightwalker – Fotona, o que foi devidamente explicado e incluído no TCLE, além de mudanças no protocolo, justificadas por evidências apresentadas. Entre essas mudanças está o intervalo de 14 dias (antes variando entre 14 e 28 dias) e a utilização de um pré-tratamento com ser Nd:YAG, comprimento de onda de 1.064 nm,modo VLP, para promover sensibilização tecidual não ablativa da região a ser tratada, no grupo tratado com o equipamento Lightwalker Fotona. Todas as alterações propostas também estão contempladas no TCLE a ser aplicado aos participantes.

Considerações sobre os Termos de apresentação obrigatória:

Verificar item Conclusões ou Pendências e Lista de Inadequações.

Recomendações:

Verificar item Conclusões ou Pendências e Lista de Inadequações.

Conclusões ou Pendências e Lista de Inadequações:

A emenda apresentada não apresenta óbices éticos.

Considerações Finais a critério do CEP:

Ressalta-se que cabe ao pesquisador responsável encaminhar os relatórios parciais e final da pesquisa, por meio da Plataforma Brasil, via notificação do tipo "relatório" para que sejam devidamente apreciados no CEP, conforme Norma Operacional CNS no 001/13, item XI.2.d..Qualquer alteração no projeto original deve ser apresentada "EMENDA",por meio da Plataforma Brasil, de forma objetiva e com justificativas para nova apreciação (Norma Operacional 001/2013 – letra H).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento Arquivo Informações Básicas PB_INFORMAÇÕES_BÁSICAS_183150 do Projeto 0_E1.pdf

Postagem Autor 27/09/2021 22:06:19

Situação Aceito

Endereço: Av Prof Lineu Prestes 2227 – 1° andar , sala 02 da administração

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Continuação do Parecer: 5.019.423

Outros

Brochura Pesquisa Cronograma

Projeto Detalhado / Brochura Investigador Outros

Folha de Rosto

Declaração de Instituição e Infraestrutura

Situação do Parecer:

Aprovado

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VALERIA MENDES

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169

Justificativa de Ausência				

.

Necessita Apreciação da CONEP:

Não

SAO PAULO, 05 de Outubro de 2021

Assinado por:

Alyne Simões Gonçalves (Coordenador(a))

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Anexo 2 – Termo de Consentimento Livre e Esclarecido

Termo de Consentimento Livre e Esclarecido (TCLE) para participação na pesquisa

Título: Avaliação clínica do uso do laser de érbio no distúrbio do ronco

Nome dos Pesquisadores: Valeria Mendes, Denise Maria Zezell, Luciane Hiramatsu Azevedo

Local: Faculdade de Odontologia da Universidade de São Paulo (Laboratório Especial de Laser na Odontologia – LELO)

Convite: Convidamos a participar nessa pesquisa que tem por finalidade a avaliar clinicamente o uso do laser de érbio no tratamento do ronco.

Participante da pesquisa: Sua participação é voluntária e este consentimento poderá ser retirado a qualquer momento, sem prejuízos à continuidade do tratamento.

Justificativa para a pesquisa: As doenças respiratórias do sono estão relacionadas com maior risco de pressão alta, infarto, AVC, diabetes e uso de medicamentos. O ronco é o estágio inicial da apneia obstrutiva do sono (AOS), doença complexa e evolutiva, bastante comum na população mundial. Os tratamentos atuais envolvem procedimentos cirúrgicos com hospitalização e pós-operatório doloroso ou não cirúrgicos, mas dependentes de engajamento e aderência do paciente para que se alcance o resultado esperado. Há necessidade de abordagens precoces de tratamento, não invasivas e eficazes.

Objetivos do estudo: avaliar se o tratamento com laser de érbio em ambulatório, que dispensa uso anestesia e internação, pode representar uma alternativa aos tratamentos para ronco existentes, melhorando o fluxo de ar durante a respiração.

Tempo e Local: Você deve comparecer à clínica do Laboratório Especial de Laser em Odontologia da Faculdade de Odontologia da Universidade de São Paulo para um pré-atendimento e também, a três sessões para avaliação de 3, 6 e 12 meses após tratamento. Para o tratamento com uso do laser, você deverá comparecer em três sessões de 20 a 30 minutos e intervalo de 14 dias entre elas, na sede da Fotona Brasil, na Rua Desembargador Eliseu Guilherme, 69 – Paraíso, São Paulo.

Grupos de estudo: Consideramos como participantes não tratados para o ronco e apneia, todos aqueles que ao receberem o diagnóstico médico indicativo de sua condição de saúde bem como as opções de tratamento e decidiram de forma consciente a não aderir às mesmas ou ainda, as abandonaram por conta própria, depois de alguma tentativa sem êxito. Para os participantes que já tiverem iniciado o tratamento, não será necessária a interrupção ou suspensão deste já iniciado.

Caso o tratamento com laser se mostre positivo, existe a possibilidade de que a terapia inicial necessite de um ajuste. Para os casos de uso do aparelho intraoral de avanço mandibular, talvez seja necessário um ajuste para diminuir o avanço e isto seria bem-vindo. Para aqueles que fazem uso de Cpap, talvez seja necessária a diminuição da pressão de ar, o que ofereceria maior conforto respiratório. O pesquisador responsável se compromete a informar e orientar o participante caso isso seja necessário.

Serão atendidos para esta pesquisa 45 participantes, distribuídos de forma aleatória em 3 grupos de 15 participantes cada um. O grupo de controle e dois grupos experimentais. Existe a possibilidade de que você seja incluído em qualquer um desses três grupos.

Grupo 1 – grupo controle: Participando deste grupo, você não receberá o tratamento, mas será atendido da mesma forma, ou seja, para simular o laser real, será usada uma luz não funcionante. Assim como você, o avaliador dos resultados desta pesquisa também não saberá quem participou do grupo controle e quem participou dos grupos experimentais. Estudos como este são chamados de estudos duplos-cegos e tem o objetivo de eliminar possíveis fontes de viés (quando olhamos para algo, de forma tendenciosa e de acordo com nossa expectativa). Quando paciente, equipe de saúde e avaliador sabem qual tratamento está sendo utilizado, todos eles têm expectativas sobre o resultado, o que os influencia sobre o que observam. Esta é, portanto, a forma mais apropriada de se fazer essa verificação. Se ficar comprovada de forma positiva a utilização do laser para tratamento do ronco, os pacientes deste grupo receberão o tratamento que apresentar o melhor resultado clínico.

Grupo 2 – grupo experimental: Se estiver participando deste grupo, você será atendido para tratamento do ronco com o equipamento Fotona. O laser de neodímio, com comprimento de onda de 1064 nm, em modo VLP será usado num primeiro momento, com o objetivo de criar uma condição de melhor aproveitamento do tratamento com o laser de érbio, no modo LP, utilizado na sequencia.

Grupo 3 – grupo experimental: Se participando deste grupo, você será atendido para tratamento do distúrbio do ronco com o equipamento LiteTouch no modo *gentil*.

Durante o estudo, você não terá ciência de qual grupo é pertencente.

Motivação para desenho da pesquisa com dois grupos utilizando o mesmo tipo de laser, de fabricantes diferentes: O equipamento Fotona, da Eslovênia é líder no mercado de laser de érbio. A empresa desenvolveu uma ponteira e um protocolo para tratamento do ronco, que utilizamos em um dos grupos, para verificar o resultado clínico na população brasileira. O equipamento LiteTouch, de Israel, chegou ao Brasil mais recentemente e tem ganhado espaço no cenário nacional. Utilizaremos este equipamento em outro grupo, para verificar se os resultados obtidos com seu uso, podem se equiparar aos resultados obtidos com o primeiro equipamento. Se os resultados se mostrarem positivos, a publicação deste estudo poderá embasar a possibilidade de se tratar o ronco pelos dois equipamentos, atingindo assim uma parcela maior da população.

Procedimento:

Pré-atendimento: Neste dia, deve-se apresentar o exame previamente realizado de polissonografia, para registro na ficha da pesquisa, dos dados avaliados no exame.

Avaliação geral de saúde, percepção do ronco, sonolência e qualidade do sono serão avaliados por questionários. Serão registradas as medidas de circunferência do pescoço, da cintura e índice de massa corporal (por meio de registro de peso e altura). Durante uma noite, em sua própria casa, o ronco será medido e gravado, e os seus dados de saúde (frequência cardíaca e quantidade de oxigênio no sangue) serão registrados em um exame do sono (chamado polissonografia tipo IV), por meio de smartphone, um equipamento de oximetria de alta resolução e software específico, cedidos a você nessa ocasião, para essa finalidade. O registro destes parâmetros, assim como das imagens obtidas da fotografia do interior de boca realizada antes do uso do laser, servirá como base para comparação ao final do estudo. Neste dia serão marcadas suas próximas consultas.

Atendimento: Você deve comparecer à sede da FOTONA BRASIl na Rua Desembargador Eliseu Guilherme, 69 – Paraíso, São Paulo – em 03 sessões de 20 a 30 minutos. Nestes dias, serão realizadas fotos do interior da boca antes e após o uso do laser:

1º atendimento com uso de laser;

2º atendimento com uso de laser: após 14 dias do 1º atendimento para tratamento;

3º atendimento com uso de laser: após 28 dias do 1º atendimento para tratamento.

Consultas de acompanhamento de 3, 6 e 12 meses: Você deve comparecer à clínica do Laboratório Especial de Laser em Odontologia da Faculdade de Odontologia da Universidade de São Paulo, para avaliação de percepção do ronco, sonolência e qualidade do sono feita por questionários. Serão registradas medidas de circunferência do pescoço, da cintura e índice de massa corporal, serão realizadas fotos do interior da boca. Durante uma noite, em sua própria casa, o ronco será medido e gravado e os seus dados de saúde (frequência cardíaca e quantidade de oxigênio no sangue) serão registrados em um exame do sono (chamado polissonografia tipo IV), por meio de smartphone, um equipamento de oximetria de alta resolução e software específico, cedidos a você nessa ocasião, para essa finalidade.

O registro dos parâmetros e imagens obtidos após o último atendimento com laser serão denominados nesta pesquisa como registros finais e serão utilizados para comparação com os registros inicias do estudo.

O registro dos parâmetros dos retornos de 3, 6 e 12 meses será utilizado para comparação com os registros iniciais e finais do estudo para analisar o resultado obtido com o tratamento, ao longo do tempo.

Procedimento para o tratamento: será utilizado o laser de érbio, com comprimento de onda de 2940nm (Lightwalker Fotona, Ljubljana, Slovenia ou LiteTouch – Light Instruments Ltd., Israel) em modo *LP* ou *gentil,* respectivamente. Serão três sessões de atendimento com uso de laser. Os parâmetros definidos para o tratamento seguem as indicações dos fabricantes, mas pequenas adaptações de condição de irradiação poderão ser necessárias. O número de pulsos por atendimento é variável, pois depende das características anatômicas de cada pessoa. Não se faz necessária medicação pré-tratamento ou anestesia. O participante da pesquisa e o operador utilizarão óculos de proteção para proteger os olhos da irradiação do laser. A região chamada de orofaringe (que compreende estruturas internas da boca e do início da garganta, por onde o ar passa durante nossa respiração) recebe a luz do laser. O equipamento fica a uma distancia de aproximadamente dois centímetros dessas regiões (não há necessidade de encostar o equipamento). Como recomendações pós-tratamento, os pacientes podem retomar a rotina de vida deles imediatamente. Nenhum cuidado especial após o tratamento com o laser é necessário.

Benefícios: O estudo avalia se o uso do laser de érbio pode trazer benefícios no tratamento do ronco e você tem a possibilidade de ter seu ronco diminuído ou eliminado, melhorando a qualidade do sono. Se os resultados forem positivos, no futuro, essa terapia pode representar uma nova abordagem de tratamento, contribuindo para a redução de doenças crônicas e uso de medicamentos, para a melhora da qualidade do sono e consequentemente da qualidade de vida das pessoas.

Riscos e desconfortos: O estudo pode trazer como risco para você, o fato de a terapia não ter o efeito desejado ou ter efeito transitório. Como desconforto, pode ocorrer a sensação de incômodo local, por sensação de calor

leve, na região que recebe a luz. O pesquisador responsável se compromete a suspender a pesquisa imediatamente ao perceber que você sente qualquer desconforto decorrente do estudo. O pesquisador e a instituição assumem a responsabilidade de dar assistência integral a qualquer complicação e danos que por ventura possam ocorrer.

Avaliação dos desfechos: Como principal resultado clínico, espera-se responder à pergunta da pesquisa: O tratamento do distúrbio do ronco com o uso do laser de érbio amplia o volume das vias aéreas superiores (VAS), que compreende estruturas internas do nariz, boca e do início da garganta, por onde o ar passa durante nossa respiração facilitando a passagem do ar durante a respiração, em procedimento ambulatorial sem complicações significativas? O resultado do tratamento leva à melhora na qualidade do sono, no distúrbio do ronco e sonolência diurna analisadas? Contribui com a melhora dos parâmetros de saúde observados por meio dos exames realizados?

A avaliação de volume das vias aérea superiores será realizada por comparação da classificação de Mallampati modificada, registrada por fotografia do interior de boca, antes e após cada atendimento com o uso do laser, e também nas consultas de acompanhamento de 3, 6 e 12 meses, levando em consideração a faixa etária, o gênero, o índice de massa corporal (IMC – que é uma medida que relaciona o seu peso com sua altura), medidas de circunferência do pescoço, padrão oclusal, consumo de medicamentos e presença de apneia.

Os dados coletados por meio dos questionários, fichas, gravações e exames, realizados e registrados antes e depois do atendimento com o uso do laser e também nas consultas de acompanhamento, avaliam os seus dados de saúde (frequência cardíaca e quantidade de oxigênio no sangue) e dados do seu ronco, como tempo de sono com ronco e volume do ruído; sonolência diurna e qualidade do sono; percepção do ronco pelo paciente e pelo(a) parceiro(a) de quarto se houver, satisfação com o resultado e existência de desconfortos e/ou efeitos adversos com o tratamento de laser de érbio para o distúrbio do ronco.

Ajuda de custo: Não haverá ajuda de custo aos voluntários participantes dessa pesquisa. Também não haverá nenhuma forma de pagamento pela sua participação.

Ressarcimento: Sua participação no estudo não implicará em custos adicionais. Isto quer dizer que você não terá qualquer despesa com a realização dos procedimentos previstos neste estudo. Quando houver necessidade de deslocamento apenas para fins deste estudo, o participante da pesquisa e seu(s) acompanhante(s), quando necessário, serão ressarcidos.

Métodos terapêuticos alternativos: Atualmente, as modalidades de tratamento envolvem a realização de cirurgias na região da garganta, uso do Cpap (aparelho que faz um fluxo pressurizado e contínuo de ar pelo nariz), uso de aparelhos colocados nos dentes para modificar a posição da boca durante o sono, os exercícios de fonoaudiologia para fortalecimento dos músculos da garganta, e a combinação de dieta com exercícios físicos para reduzir o peso.

Acesso ao prontuário: É assegurado ao participante da pesquisa o acesso aos dados contidos no prontuário após a finalização da pesquisa.

Assistência em virtude de danos decorrentes da pesquisa: Asseguramos que o participante da pesquisa receberá assistência integral e imediata, de forma gratuita pelo tempo que for necessário em caso de danos decorrentes da pesquisa.

Indenização: Asseguramos que o participante da pesquisa tem direito a indenização em caso de danos decorrentes do estudo.

Garantia do sigilo da identidade do participante da pesquisa: As informações fornecidas serão responsabilidade dos pesquisadores. Os participantes da pesquisa não serão identificados em nenhum momento, mesmo quando os resultados desta pesquisa forem divulgados em qualquer forma.

Reutilização dos dados: Perguntamos se o participante da pesquisa autoriza a utilização dos dados em outras pesquisas:

( ) NÃO autorizo a utilização de dados em outra pesquisa

( ) SIM autorizo a utilização de dados

( ) NÃO quero ser consultado da utilização dos meus dados em outra pesquisa, desde que a nova pesquisa seja aprovada pelo Comitê de Ética em Pesquisa

( ) SIM quero ser consultado da utilização dos meus dados

Liberdade de recusa em participar do estudo: Asseguramos que o participante da pesquisa tem plena liberdade de se recusar a participar do estudo a qualquer momento da pesquisa e que esta decisão não gerará penalização por parte dos pesquisadores.

Liberdade de retirada do consentimento: Asseguramos que o participante da pesquisa tem plena liberdade de retirar o seu consentimento a qualquer momento da pesquisa e que esta decisão não gerará penalização por parte dos pesquisadores.

Direito de desistir do estudo: Os participantes da pesquisa poderão desistir do estudo a qualquer momento sem nenhuma penalidade e sem perder os benefícios aos quais tenha direito. Os participantes da pesquisa receberão a assistência que for adequada, de forma gratuita, pelo tempo que for necessário.

Direito de desistir do tratamento: Os participantes da pesquisa poderão desistir do tratamento a qualquer momento sem nenhuma penalidade e sem perder os benefícios aos quais tenha direito como acompanhamento e assistência.

Fornecimento de uma via original do documento com assinatura e rubricas:
Asseguramos que o participante da pesquisa receberá uma via do documento, assinada pelo participante da pesquisa (ou seu representante legal) e pelo pesquisador responsável e rubricada em todas as páginas por ambos.

Pesquisadora responsável: Valeria Mendes (CRO 56166) – telefones: (11) 4154.4424 ou (11) 99538.7318, email: valeria.m@ipen.br; Professora orientadora: Profa. Dra. Denise maria Zezell – telefones: (11) 3133.9370 ou (11) 99659.0714, email: zezell@usp.br; Professores colaboradores: Profa. Dra. Luciane Hiramatsu Azevedo (CRO 57630) – telefones: (11) 3091.7645 ou (11) 99728.8175, email: luazevedo@usp.br.

Neste período atípico de isolamento social, o **CEP-FOUSP** não está fazendo atendimento presencial. Entretanto, suas dúvidas sobre a ética da pesquisa, poderão ser encaminhadas ao email: cepfo@usp.br que serão respondidas o mais breve possível ou pelo telefone: (11) 3091.7960. O comitê é um colegiado interdisciplinar e independente, de relevância pública, de caráter consultivo, deliberativo e educativo, criado para defender os interesses dos participantes da pesquisa em sua integridade e dignidade, para contribuir no desenvolvimento da pesquisa dentro de padrões éticos (Resolução CNS no. 466 de 2012). Situa-se à Av. Prof. Lineu Prestes, 2227, Cidade Universitária, São Paulo -SP.

Após ler essas informações e de ter minhas dúvidas suficientemente esclarecidas pelo pesquisador, concordo em participar de forma voluntária neste estudo.

Nome do participante da pesquisa: _____

Endereço: _____

Telefone para contato: (____) _____

Local e data: _____

Assinatura do participante da pesquisa: _____

_____

Assinatura dos pesquisadores: _____. _____.

Valeria Mendes   Profa. Dra. Denise Maria Zezell

Pesquisadora responsável   Orientadora

Anexo 3 – Questionário de anamnese

Questionário de Saúde – Anamnese para o estudo de avaliação clínica do uso do laser no distúrbio do ronco

Pesquisadora responsável: Valeria Mendes – Cirurgiã-Dentista especialista em OPNE – CRO 56166

A participação neste estudo é voluntária e todos os dados serão colhidos e tratados forma anônima

O presente questionário atende as exigências legais e terapêuticas e tem por finalidade ajudar o profissional a conhecer aspectos de sua saúde geral que podem influenciar no seu tratamento. O que você declarar neste questionário torna-se informação confidencial, guardada por força de sigilo profissional (Art.9 do código de ética). Você, paciente, é responsável em casos de omissões ou falsas informações.

Nome:_____

Data de nascto: ____/____/_____Estado civil:_____ Profissão:_____

RG.:_____ CPF.: _____idade: _____

Endereço Residencial:_____

Cidade/Estado:_____ Email: _____

Tel resid.:_____Tel coml.: _____Tel cel.:_____

Está sob tratamento médico? ( )sim ( )não Qual? _____

Nome do médico:_____tel.: _____

Tem alguma alergia? ( )sim ( )não Qual?_____

Já fez uso de cortisona ou esteróides? ( )sim ( )não Qto tempo? _____

Já fez tratamento hormonal? ( )sim ( )não Qto tempo? _____

Para mulheres: Está grávida ou amamentando? ( )sim ( )não

Toma anticoncepcional? ( )sim ( )não Qual? _____

Há qto tempo? ___

Já passou por avaliação médica nas seguintes áreas:

Endocrinologia ( )sim ( )não;   Otorrinolaringologia ( )sim ( )não;

Neurologia ( )sim ( )não;   Psiquiatria ( )sim ( )não;

Cardiologia ( )sim ( )não;   Medicina do Sono ( )sim ( )não;

Realiza atividade física? ( )sim ( )não; Qual? _____

Com que frequência? _____

Responda abaixo se apresenta ou não alguma das condições de saúde e, em caso afirmativo, informe a medicação em uso para cada problema:

hipertensão arterial ( )sim ( )não _____

doença pulmonar ( )sim ( )não_____

asma/bronquite ( )sim ( )não _____

obstrução nasal – eventual ou constante? ( )sim ( )não _____

triglicérides/colesterol elevados ( )sim ( )não _____

diabetes ( )sim ( )não _____

epilepsia/convulsões ( )sim ( )não _____

doença renal ( )sim ( )não _____

hepatite ou outra doença do fígado ( )sim ( )não _____

úlcera/refluxo/gastrite ( )sim ( )não _____

reumatismo/febre reumática ( )sim ( )não _____

hipotireoidismo/hipertireoidismo ( )sim ( )não _____

menopausa/faz reposição hormonal? ( )sim ( )não _____

depressão/ansiedade ( )sim ( )não _____

distúrbios neurológicos ( )sim ( )não _____

artrite óssea, distúrbio muscular ou articular ( )sim ( )não _____

DST, AIDS ( )sim ( )não _____

cancer ( )sim ( )não Onde? _____

Já fez quimioterapia ou radioterapia? ( )sim ( )não Quando? _____

já utilizou drogas ilícitas? ( )sim ( )não

Qual tipo, dose e frequência _____

Fuma? ( )sim ( )não quanto?_____

Bebe? ( )sim ( )não _____ quanto? _____

Faz uso de medicação fotossensível? ( )sim ( )não;

Qual? _____

Já apresentou alguma complicação após tratamentos médicos ou odontológicos? ( )sim ( )não

Explique: _____
_____

Faz uso de algum tratamento para ronco e/ou apneia? ( )sim ( )não;

Qual? _____

Relate alguma doença ou fato importante sobre sua saúde que não conste neste questionário:

_____
_____

Declaro que todas as informações por mim fornecidas neste questionário são verdadeiras. Entendi todas as perguntas e nada omiti.

São Paulo, _____ de _____ de _____.

_____

Assinatura

Anexo 4 – Questionário de Berlim (BQ) – sobre a percepção do ronco.

Questionário de Berlim

NOME: _____

RG.:_____ TEL.: _____

DATA: _____

QUESTIONÁRIO DE BERLIM

CATEGORIA 1

1- Você ronca? (   )Sim;   (   ) Não;   (   ) Não sei

2- Seu ronco é? (   )Pouco mais alto que respirando;
                    (   )Tão alto quanto falando;
                    (   )Mais alto que falando;
                    (   )Muito alto que pode ser ouvido nos quartos próximos

3- Com que frequência você ronca?

(   )Praticamente todos os dias;   (   )1-2 vezes por semana;
(   )3-4 vezes por semana;   (   )Nunca ou praticamente nunca

4- O seu ronco incomoda alguém? (   )Sim;   (   ) Não

5- Alguém notou que você para de respirar enquanto dorme?

(   )Praticamente todos os dias;   (   )1-2 vezes por semana;
(   )3-4 vezes por semana;   (   )Nunca ou praticamente nunca

CATEGORIA 2

6- Quantas vezes você se sente cansado ou com fadiga depois de acordar?

(   )Praticamente todos os dias;   (   )1-2 vezes por semana;
(   )3-4 vezes por semana;   (   )Nunca ou praticamente nunca

7- Quando você está acordado, você se sente cansado, fadigado ou não se sente bem?

(   )Praticamente todos os dias;   (   )1-2 vezes por semana;
(   )3-4 vezes por semana;   (   )Nunca ou praticamente nunca

8- Alguma vez você cochilou ou caiu no sono enquanto dirigia?

(   )Sim; (   ) Não

CATEGORIA 3

9- Você tem pressão alta? (   )Sim;   (   ) Não;   (   ) Não sei

Anexo 5 – Questionário de Epworth (ESSE) – sobre sonolência diurna.

Questionário de Epworth para Avaliação da Sonolência Diurna

NOME: _____

RG.:_____ TEL.: _____

ESCALA DE SONOLÊNCIA DE EPWORTH

Qual a probabilidade de você cochilar ou adormecer nas situações abaixo e não apenas sentir-se cansado?

Este questionário refere-se ao modo de vida habitual nos últimos tempos. Mesmo que não tenha passado por alguma dessas situações ultimamente, tente imaginar como é que elas o(a) afetariam. Use a escala que segue para escolher o número mais apropriado de cada situação:

0 - nenhuma - probabilidade de pegar no sono
1 - ligeira - probabilidade de pegar no sono
2 - moderada - probabilidade de pegar no sono
3 - forte - probabilidade de pegar no sono

situação	probabilidade de pegar no sono
sentado lendo um livro	
sentado vendo televisão	
sentado inativo em lugar público (sala de espera, cinema, reunião)	
como passageiro em um carro, durante uma hora sem parada	
deitado, descansando à tarde, quando as circunstâncias permitem	
sentado conversando com alguém	
sentado calmamente após um almoço sem ter bebido álcool	
ao volante, parado no trânsito por alguns minutos	

Data: _____   Soma dos pontos: _____

Anexo 6 – Questionário de Pittsburgh – sobre a qualidade do sono

Questionário De Qualidade De Sono De Pittsburgh

Nome: _____

Idade:_____ Data:_____

Instruções:

As seguintes perguntas são relativas aos seus hábitos de sono durante o último mês somente. Suas respostas devem indicar a lembrança mais exata da maioria dos dias e noites do último mês. Por favor, responda a todas as perguntas.

1. Durante o último mês, quando você geralmente foi para a cama à noite? Hora usual de deitar
_____

2. Durante o último mês, quanto tempo (em minutos) você geralmente levou para adormecer à noite? Número de minutos _____

3. Durante o último mês, quando você geralmente levantou de manhã? Hora usual de levantar
_____

4. Durante o último mês, quantas horas de sono você teve por noite? (Este pode ser diferente do número de horas que você ficou na cama). Horas de sono por noite _____

Para cada uma das questões restantes, marque a melhor (uma) resposta. Por favor, responda a todas as questões.

5. Durante o último mês, com que frequência você teve dificuldade de dormir porque você:

(a) **Não conseguiu adormecer em até 30 minutos**:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(b) **Acordou no meio da noite ou de manhã cedo**:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(c) **Precisou levantar para ir ao banheiro**:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(d) Não conseguiu respirar confortavelmente:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(e) Tossiu ou roncou forte:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(f) Sentiu muito frio:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(g) Sentiu muito calor:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(h) Teve sonhos ruins:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(i) Teve dor:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(j) Outra (s) razão (ões), por favor, descreva:

_____

_____

Com que frequência, durante o último mês, você teve dificuldade para dormir devido a essa razão?

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

6. Durante o último mês, como você classificaria a qualidade do seu sono de uma maneira geral?

Muito boa (   );   Boa (   );   Ruim (   );   Muito ruim (   )

7. Durante o último mês, com que frequência você tomou medicamento (prescrito ou "por conta própria") para lhe ajudar a dormir?

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

8. No último mês, com que frequência você teve dificuldade de ficar acordado enquanto dirigia, comia ou participava de uma atividade social (festa, reunião de amigos, trabalho, estudo)?

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

9. Durante o último mês, quão problemático foi para você manter o entusiasmo (ânimo) para fazer as coisas (suas atividades habituais)?

Nenhuma dificuldade (   );   Um problema leve (   );
Um problema razoável (   );   Um grande problema (   );

10. Você tem um(a) parceiro [esposo(a)] ou colega de quarto?

Não (   );   Parceiro ou colega, mas em outro quarto (   );
Parceiro no mesmo quarto, mas não na mesma cama (   );   Parceiro na mesma cama (   );

Se você tem um parceiro ou colega de quarto, pergunte a ele/ela com que frequência, no último mês, você teve...

(a) Ronco forte

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(b) Longas paradas na respiração enquanto dormia

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(c) Contrações ou puxões nas pernas enquanto você dormia

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(d) Episódios de desorientação ou confusão durante o sono

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

(e) Outras alterações (inquietações) enquanto você dorme; por favor descreva:

Nenhuma no último mês (   )

Menos de 1 vez/ semana (   )

1 ou 2 vezes/ semana (   )

3 ou mais vezes/ semana (   )

Anexo 7 – Instruções para o exame de polissonogrfia – como baixar o aplicativo e realizar o exame
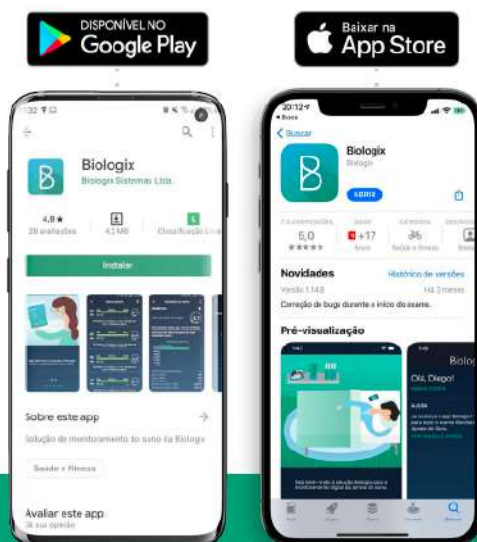
3

Realizando exame

Após realizar o login com seu CPF e senha cadastrado, para iniciar o exame, basta pressionar:
"Novo exame" →
Autorização →
Responda o questionário
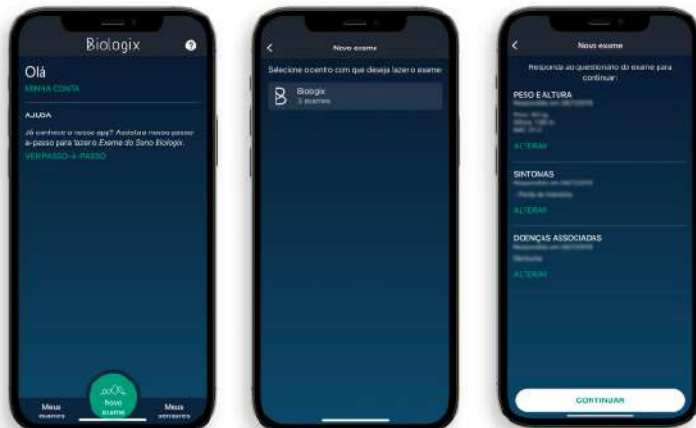
Assim que logado em sua conta, para dar início ao exame, pressione o botão verde "novo exame".

Em seguida, clique na autorização emitida pelo centro credenciado responsável pelo seu exame.

O próximo passo é preencher todos os campos do questionário. Lembre de colocar os dados corretamente.

4

Exame iniciado:

- Manter o smartphone próximo do sensor durante todo o exame.
- Se precisar pausar o exame por qualquer motivo, retire o sensor do dedo sem mexer no aplicativo.
- Ao recolocar o sensor no dedo o exame será retomado.
- Se o sensor ficar fora do dedo por mais de 30 minutos, o exame será automaticamente encerrado, mas será necessário concluir o exame no aplicativo.
- Lembrando que é necessário possuir conexão com a internet para iniciar e concluir o exame.

5 Concluindo o exame

- Ao acordar pela manhã, o(a) paciente deve acessar o aplicativo e pressionar CONCLUIR. Nesse momento é necessário que o smartphone esteja conectado à internet.
- Um exame só será considerado válido quando sua duração for de no mínimo 4 horas.
- Retirar o sensor do dedo
- Guardar o sensor no estojo
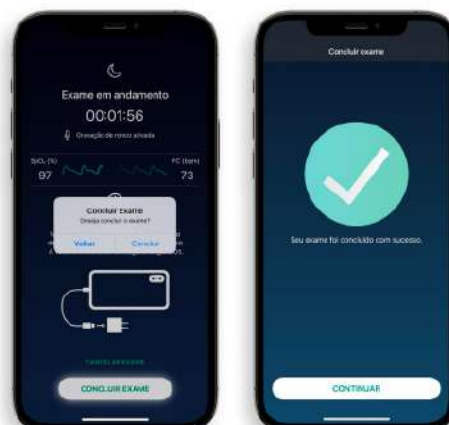
Anexo 8 – Laudo do exame de polissonografia realizado.
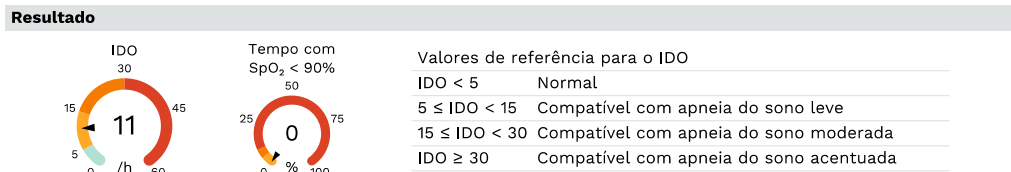
Biologix

Exame do Sono Biologix

Centro credenciado

Dra. Valeria Mendes - Cecom Odontologia	Telefone	▮▮▮▮

Paciente

Nome	▮▮▮▮
Data de nasc.	07/07/1966 (56 anos)
Sexo	Feminino

Exame

Início	30/09/2022 – 03:14:08
Fim	30/09/2022 – 07:16:08
Tempo total	04:02:00 (242,0 min)
Tempo válido	03:46:27 (226,5 min)

Condições na noite do exame

○ Consumo de álcool
○ Congestão nasal
○ Sedativos
● *Nenhuma*

Tratamentos na noite do exame

○ CPAP
○ Aparelho de avanço
● *Nenhum*

Questionário do exame

Peso e altura	Sintomas	Doenças associadas
Respondido em 24/01/2022	Respondido em 24/01/2022	Respondido em 24/01/2022

Peso e altura		Sintomas	Doenças associadas
Peso	86 kg	● Ronco alto e frequente	○ Hipertensão arterial sistêmica
Altura	1,69 m	○ Dificuldade para manter o sono	○ Doença arterial coronária
IMC	30,1	○ Sono agitado	○ Insuficiência cardíaca
		○ Sono não reparador	○ Arritmia cardíaca
		● Sonolência ou cansaço diurno	○ Acidente vascular cerebral (AVC)
		○ Diminuição da libido ou disfunção erétil	○ Diabetes
		● Dificuldade de concentração	○ Depressão
		● Perda de memória	○ Refluxo gastroesofágico
		○ *Nenhum*	○ Doença respiratória
			● *Nenhuma*

Resultado

IDO **11** /h

Tempo com SpO$_2$ < 90% **0** %

Valores de referência para o IDO	
IDO < 5	Normal
5 ≤ IDO < 15	Compatível com apneia do sono leve
15 ≤ IDO < 30	Compatível com apneia do sono moderada
IDO ≥ 30	Compatível com apneia do sono acentuada

Exame de polissonografia tipo IV realizado no dia 30/09/2022, iniciado às 03:14 e terminado às 07:16. O tempo total de registro foi de 4h02min (242 minutos) e o tempo válido foi de 3h46min (226 minutos). Foram monitorados os seguintes canais: oximetria de alta resolução, frequência cardíaca, movimento por actimetria e áudio para análise de ronco. Foram observadas 40 dessaturações de oxigênio durante o registro, com IDO de 10,6/hora (normal: inferior a 5/hora). A saturação da oxi-hemoglobina (SpO$_2$) teve valor médio de 94% e não permaneceu abaixo de 90% por tempo significativo. Foram detectados eventos de ronco durante 78% do tempo de registro.

Conclusão

Exame compatível com apneia do sono leve (IDO 10,6/hora), nas condições descritas.
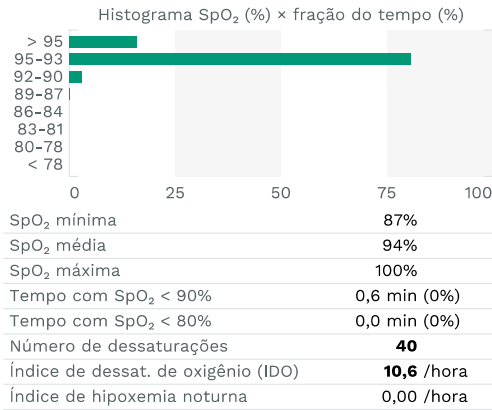
[assinatura]
5-1

Nota: considera-se uma dessaturação de oxigênio a queda temporária de pelo menos 3 pontos percentuais no nível de saturação da oxi-hemoglobina (SpO$_2$). Um evento de hipoxemia ocorre quando a SpO$_2$ permanece abaixo de 90% durante ao menos 5 minutos com um nadir de 85%. Os índices correspondem ao número de eventos dividido pelo tempo válido do exame.
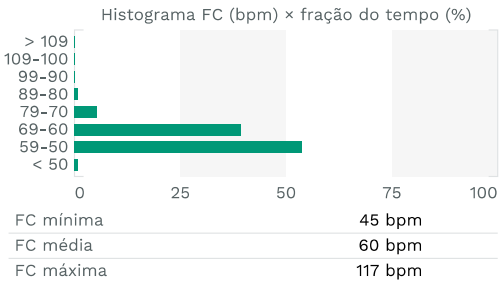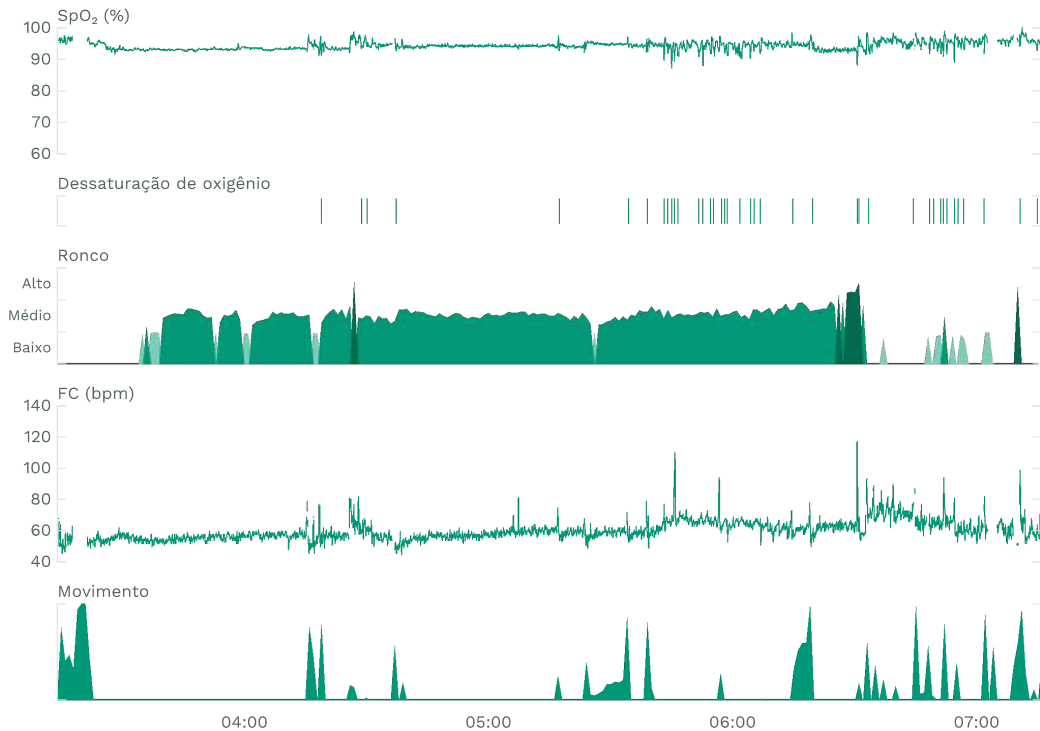
Biologix

Exame do Sono Biologix

Oximetria (SpO$_2$)

Histograma SpO$_2$ (%) × fração do tempo (%)

SpO$_2$ mínima	87%
SpO$_2$ média	94%
SpO$_2$ máxima	100%
Tempo com SpO$_2$ < 90%	0,6 min (0%)
Tempo com SpO$_2$ < 80%	0,0 min (0%)
Número de dessaturações	**40**
Índice de dessat. de oxigênio (IDO)	**10,6** /hora
Índice de hipoxemia noturna	0,00 /hora

Frequência Cardíaca (FC)

Histograma FC (bpm) × fração do tempo (%)

FC mínima	45 bpm
FC média	60 bpm
FC máxima	117 bpm

Análise de ronco

Tempo de gravação	241,0 min
Tempo com ronco	189,0 min (78%)

Silêncio	Baixo	Médio	Alto
22 %	7 %	68 %	3 %

Polissonogramas

Anexo 9 – Painel do editor de forma Adobe audtion com a representação visual das ondas sonoras, ao longo da noite de sono. No eixo x, o tempo e no eixo y, a amplitude em decibéis.
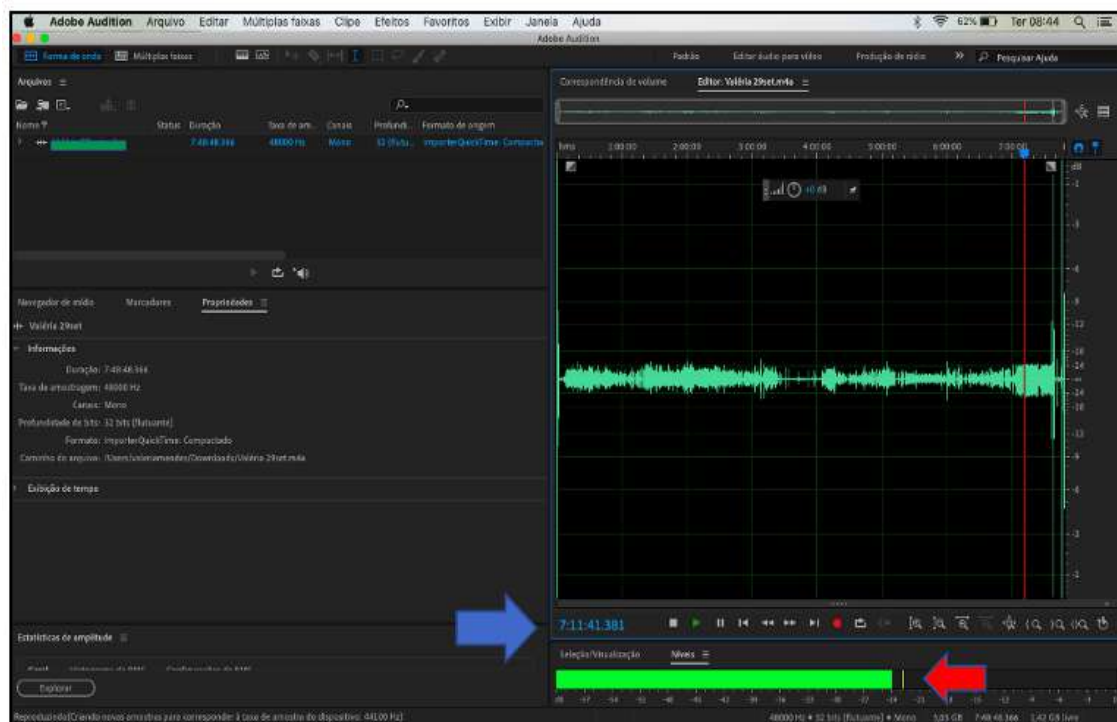
Anexo 10 – Material produzido para calibração dos avaliadores

Olá, professor X!
Uma honra para mim, contar um profissional de seu gabarito no time de avaliação de resultados do meu trabalho de mestrado. Muito obrigada pela colaboração!

Estou a disposição para esclarecer as dúvidas que surgirem. Um grande abraço e toda minha gratidão, Att., Valeria Mendes

-.-

CALIBRAÇÃO DE AVALIADORES

De acordo com publicação do Ministério da Saúde, em 2001, a calibração de examinadores é o processo que visa estabelecer padrões uniformes para o exame, determinando parâmetros aceitáveis de consistência interna e externa aos examinadores, minimizando os erros e diferenças porventura existentes quanto à habilidade na obtenção dos dados e julgamento dos mesmos; assegurar uma interpretação, entendimento e aplicação uniformes dos critérios para as doenças e condições a serem observadas e registradas e que cada examinador possa examinar dentro de um padrão consistente, minimizando variações entre os diferentes examinadores.

O processo de calibração de avaliadores segue um protocolo adaptado às necessidades deste estudo e é fundamental para evitar vieses (erros sistemáticos) de observação dos resultados. (WHO, 1993)

A avaliação dos resultados é realizada por de método de comparação de dados com o registro da linha de base. Três avaliadores independentes, cegados e calibrados para avaliação do estudo, analisam os dados coletados.

• Calibração dos avaliadores

1ₐ etapa: Treinamento teórico-prático

- Revisão dos critérios de índices aplicados e do protocolo de avaliação dos resultados investigados, por meio de documento elaborado para este fim.
- As informações contidas no projeto de estudo sobre a avaliação dos resultados, já padronizadas e sistematizadas são apresentadas aos avaliadores.

- Avaliação de conhecimento dos avaliadores: após exposição dos critérios de avaliação dos resultados e exposição de fotografias em diferentes graus de comprometimento das condições avaliadas. Com possibilidade de consulta ao material escrito do treinamento. Ao final desse processo, a avaliação é discutida e as dúvidas, esclarecidas.

2a etapa – Exames práticos e verificação final da calibração dos avaliadores

Dez por cento da amostra total é avaliada por todos os envolvidos na pesquisa (pesquisador e avaliadores independentes).

Após o exame, são montadas as matrizes para verificação das concordâncias intra-examinador e interexaminadores.

A concordância entre avaliações varia de 0 a 1:

V até 0,5 – pobre

V entre 0,5 e 0,75 – moderada

V acima de 0,75 até 0,9 – bom

V maior que 0,9 – excelente

(Ministério da Saúde, 2001) (Vilella et al., 2016)

-·-·-·-·-·-·-·-·-·-·-·-·-·--·-.

1a etapa: Treinamento teórico-prático

A. Revisão dos critérios de índices aplicados e do protocolo de avaliação dos resultados investigados

Informações teóricas sobre os dados para avaliação dos resultados do estudo

"Tratamento não-ablativo dos distúrbios respiratórios do sono com associação de dois lasers pulsados de alta intensidade: Nd:YAG e Er:YAG"

Objetivo do estudo:

Objetivo geral

Avaliar clinicamente o efeito do tratamento sequencial e não-ablativo de dois lasers pulsados de alta intensidade no distúrbio respiratório do sono e no volume das vias aéreas superiores da população brasileira.

Objetivos específicos

- Analisar a percepção da eficácia da intervenção pelos participantes da pesquisa, por meio da aplicação de questionários abordando a queixa do ronco, sonolência diurna e qualidade do sono, comparando os resultados

antes e depois da intervenção [A **eficácia** mede a relação entre o efeito da ação, e os objetivos pretendidos].

- Análise visual comparativa das vias aéreas superiores (pelo índice de Mallampati modificado) antes e após o tratamento;
- Avaliar e comparar o índice de dessaturação de oxigênio e a saturação da oxi-hemoglobina média e mínima durante o sono, bem como o tempo em que a saturação permaneceu abaixo de 90%, de cada participante, no início e final do tratamento;
- Avaliar o impacto do na amplitude do ruído e no tempo de registro de ronco durante o sono, por meio da comparação dos registros, antes e após o tratamento.

Hipóteses da pesquisa:

- O tratamento não-ablativo do distúrbio respiratório do sono com laser é capaz de diminuir a amplitude do ruído e o tempo de ronco durante o sono sem complicações significativas, além de contribuir com a melhora da qualidade sono dos pacientes, com boa aceitação da intervenção pela população brasileira;
- Diminuição da complacência tecidual com consequente aumento do espaço das vias aéreas superiores, facilitando a passagem do fluxo aéreo da respiração;
- Diminuição dos índices de dessaturação de oxi-hemoglobina, do tempo de saturação abaixo de 90%, além do tempo de sono com ronco; melhora da saturação mínima de oxi-hemoglobina.

N da pesquisa: 30

Os grupos: experimental e controle foram acompanhados para avaliação do desfecho

Desfecho

O desfecho avalia se houve melhora em:

- ampliação do volume das vias aéreas superiores (VAS), facilitando a passagem do ar durante a respiração, em procedimento ambulatorial;
- parâmetros de saúde observados por meio dos exames de polissonografia tipo IV realizados (IDO, SpO_2 média e mínima em sono; tempo de sono com $SpO_2 < 90\%$), tempo de ronco e amplitude pico do ruído;
- qualidade do sono,

- distúrbio do ronco,
- sonolência diurna.

Análise estatística: é realizada por metodologia descritiva quanti-qualitativa

Interpretação dos resultados

Classificação de Mallampati modificada – desfecho principal a ser avaliado de forma independente, por 3 avaliadores cegados para o estudo

O sistema de classificação de Mallampati, desenvolvido inicialmente para predizer a facilidade de intubação de pacientes e é visualizado com a língua protuída. Foi adaptado pela medicina do sono como método de avaliação de severidade de distúrbios respiratórios do sono em ambulatório e também para predizer a indicação das cirurgias de vias aéreas de acordo com a relação entre as várias estruturas; tamanho de língua em relação à úvula, tonsilas, palato mole e paredes orofaríngeas. A forma modificada do sistema de classificação de Mallampati é realizada com a língua posicionada no assoalho da boca e tem maior semelhança com a posição fisiológica em repouso, encontrada durante o sono e está significativamente correlacionada com a predição da gravidade da apneia obstrutiva do sono em estudo de meta-análise realizado por Friedman M e colaboradores em 2013. A forma modificada é validada como método preditor da gravidade da apneia obstrutiva do sono: **Classe I** — visualiza-se toda a parede posterior da orofaringe, incluindo o pólo inferior das tonsilas palatinas; **Classe II** — visualiza-se parte da parede posterior da orofaringe; **Classe III** — visualiza-se a inserção da úvula e o palato mole, não sendo possível evidenciar-se a parede posterior da orofaringe; **Classe IV** — visualiza-se somente parte do palato mole e o palato duro. A classe I representa a melhor condição para passagem do fluxo aéreo da respiração. A classe IV representa a pior condição para passagem do ar.

Para padronização, os registros fotográficos foram obtidos com o paciente sentado, coluna ereta, abridor de boca, língua posicionada no assoalho de boca, ao final de uma inspiração lenta e profunda.

192
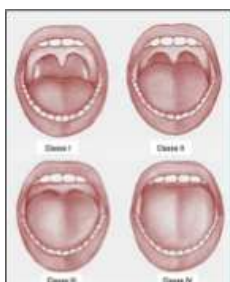
[espera-se que a classificação diminua com o tratamento (de IV até I)]

Referências: Friedman M, Hamilton C, Samuelson CG, Lundgren ME, Pott T. Diagnostic Value of the Friedman Tongue Position and Mallampati Classification for Obstructive Sleep Apnea: A Meta-analysis. *Otolaryngology–Head and Neck Surgery*. 2013;148(4):540-547. doi:10.1177/0194599812473413

Soares, Maria Claudia Mattos [UNIFESP]. Systematic evaluation value of the upper airways in presumptive diagnosing Obstructive Sleep Apnea Syndrome in an adult population in the city of São Paulo. 2015; http://repositorio.unifesp.br/handle/11600/22067 10.1016/j.sleep.2010.04.020. Epub 2010 Dec 9. PMID: 21145786.

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Avaliação de conhecimento dos avaliadores

Cada caso clínico será apresentado como o modelo a seguir. A base para comparação tem como referência a imagem e/ou dados anteriores ao tratamento.

Assim, a tabela deverá ser preenchida pelos avaliadores externos. Os campos: Antes do tratamento; depois do tratamento; retorno de 3 meses e retorno de 6 meses são preenchidos com números (1, 2, 3 ou 4) de acordo com a correspondência do grau de severidade do índice de Mallampati modificado apresentado na figura de referência. Os campos que questionam a evidência de resposta nos momentos "depois do tratamento; no retorno de 3 e de 6 meses devem ser preenchidos com o sinal positivo (+) se houver evidencia de melhora; com o sinal negativo (-) se não houver evidência de resposta ou com o sinal. A base de comparação é sempre o momento anterior ao tratamento om laser.
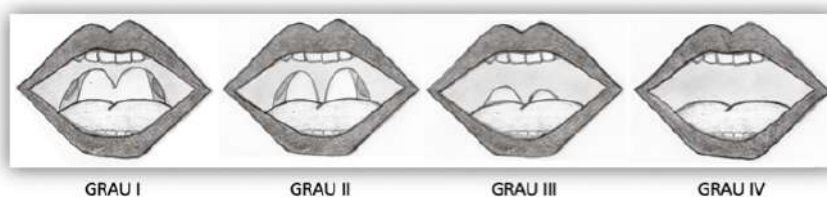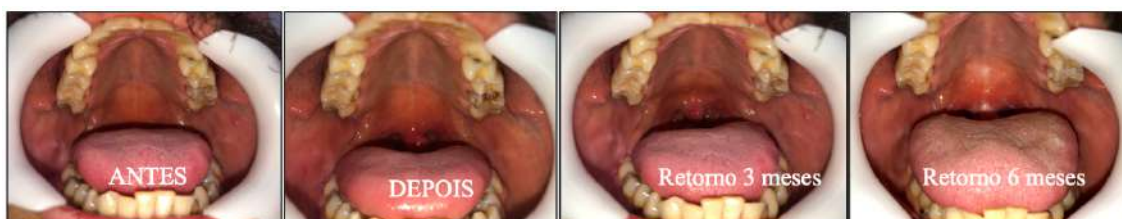
Paciente A

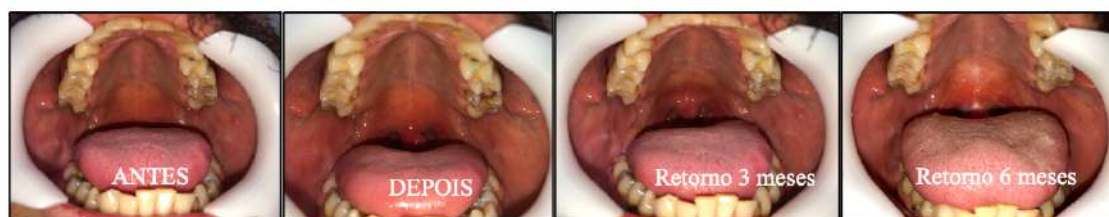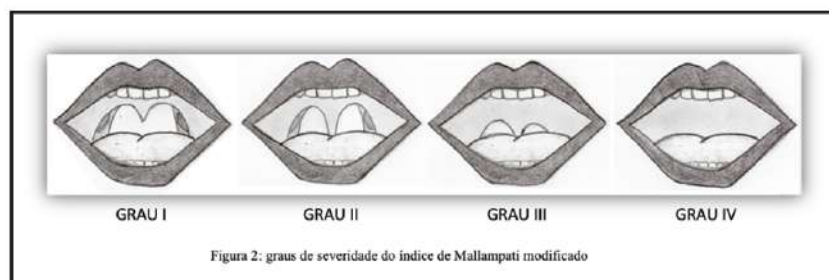Figura 2: graus de severidade do índice de Mallampati modificado

Parâmetro analisado Índice de Mallampati modificado	Antes do tratamento	Depois do tratamento	Retorno 03 meses	Retorno 06 meses	Houve melhora evidente depois do tratamento?	Há evidência de resposta no retorno de 3 meses?	Há evidência de resposta no retorno de 6 meses?
Paciente A							

2a etapa – Exames práticos e verificação final da calibração dos avaliadores

Calibração intra-examinador

Para o caso clinico a seguir, os avaliadores classificaram o caso, em dois momentos distintos, conforme o apresentado a seguir:

Figura 2: graus de severidade do indice de Mallampati modificado
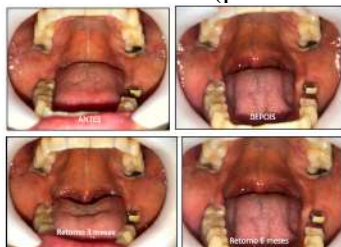

1ª avaliação do caso:

Avaliador	Parâmetro analisado Índice de Mallampati modificado	Antes do tratamento	Depois do tratamento	Retorno 03 meses	Retorno 06 meses	Houve melhora evidente depois do tratamento?	Há evidência de resposta no retorno de 3 meses?	Há evidência de resposta no retorno de 6 meses?
Dr L	PACIENTE modelo	4	2	2	3			
Dr E	PACIENTE modelo	4	3	3	4			
Dr W	PACIENTE modelo	4	3	3	2			

2ª. Avaliação do caso:

Avaliador	Parâmetro analisado Índice de Mallampati modificado	Antes do tratamento	Depois do tratamento	Retorno 03 meses	Retorno 06 meses	Houve melhora evidente depois do tratamento?	Há evidência de resposta no retorno de 3 meses?	Há evidência de resposta no retorno de 6 meses?
Dr L	PACIENTE modelo	4	2	2	1			
Dr E	PACIENTE modelo	4	3	2	3			

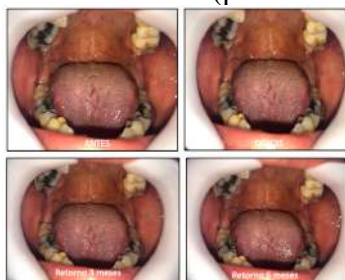| Dr W | PACIENTE modelo | 4 | 2 | 2 | 3 | | | |

Calibração inter-examinador

10% da amostra de trabalho foi apresentada. Os avaliadores classificaram o caso, conforme o apresentado a seguir:
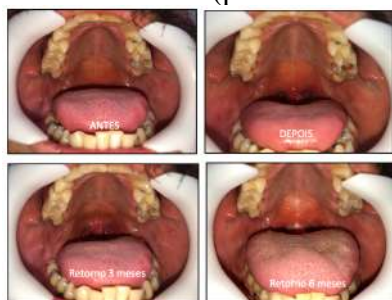
1º. Caso clinico (paciente 1 da amostra de trabalho)

Avaliador	Parâmetro analisado Índice de Mallampati modificado	Antes do tratamento	Depois do tratamento	Retorno 03 meses	Retorno 06 meses	Houve melhora evidente depois do tratamento?	Há evidência de resposta no retorno de 3 meses?	Há evidência de resposta no retorno de 6 meses?
Dr L	PACIENTE 1	4	2	2	2			
Dr E	PACIENTE 1	4	3	2	2			
Dr W	PACIENTE 1	4	2	2	2			

2º. Caso clinico (paciente 15 da amostra de trabalho)

Avaliador	Parâmetro analisado Índice de Mallampati modificado	Antes do tratamento	Depois do tratamento	Retorno 03 meses	Retorno 06 meses	Houve melhora evidente depois do tratamento?	Há evidência de resposta no retorno de 3 meses?	Há evidência de resposta no retorno de 6 meses?
Dr L	PACIENTE 15	4	4	4	4			
Dr T	PACIENTE 15	4	4	4	4			
Dr W	PACIENTE 15	4	4	4	4			

3º. Caso clinico (paciente 6 da amostra de trabalho)

Avaliador	Parâmetro analisado Índice de Mallampati modificado	Antes do tratamento	Depois do tratamento	Retorno 03 meses	Retorno 06 meses	Houve melhora evidente depois do tratamento?	Há evidência de resposta no retorno de 3 meses?	Há evidência de resposta no retorno de 6 meses?
Dr L	PACIENTE 6	4	2	2	1			
Dr T	PACIENTE 6	4	3	2	3			

Dr W	PACIENTE 6	4	2	2	3			

Como o Coeficiente de correlação intraclasse (CCI) foi superior aos 80% estipulados, toda população do estudo foi avaliada pelos avaliadores.

13 APPENDIX

When the raw data were analyzed, the Mann-Whitney test was used to compare the groups in each of the periods, while the Friedman test was used to compare the same group in the different time periods, with post hoc Wilcoxon. The significance level adopted in all tests was α = 5%. In graphs, the medians are represented by long, horizontal lines, while the mean by small squares.

Modified Mallampati Index

Table – Modified Mallampati scale for each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	4 ± 1	4 ± 1	4 ± 1	4 ± 1	0.99925
B (experiment)	4 ± 0	2 ± 2	2 ± 3	2 ± 3	0.01681
p (value)	0.80096	0.00258	0.00641	0.01432	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p. The significance detected in group B (p= 0.01681) was between the period Before and After (p= 0.00334), between Before and 3 Months (p= 0.00536) and between Before and 6 Months (p= 0.00786).
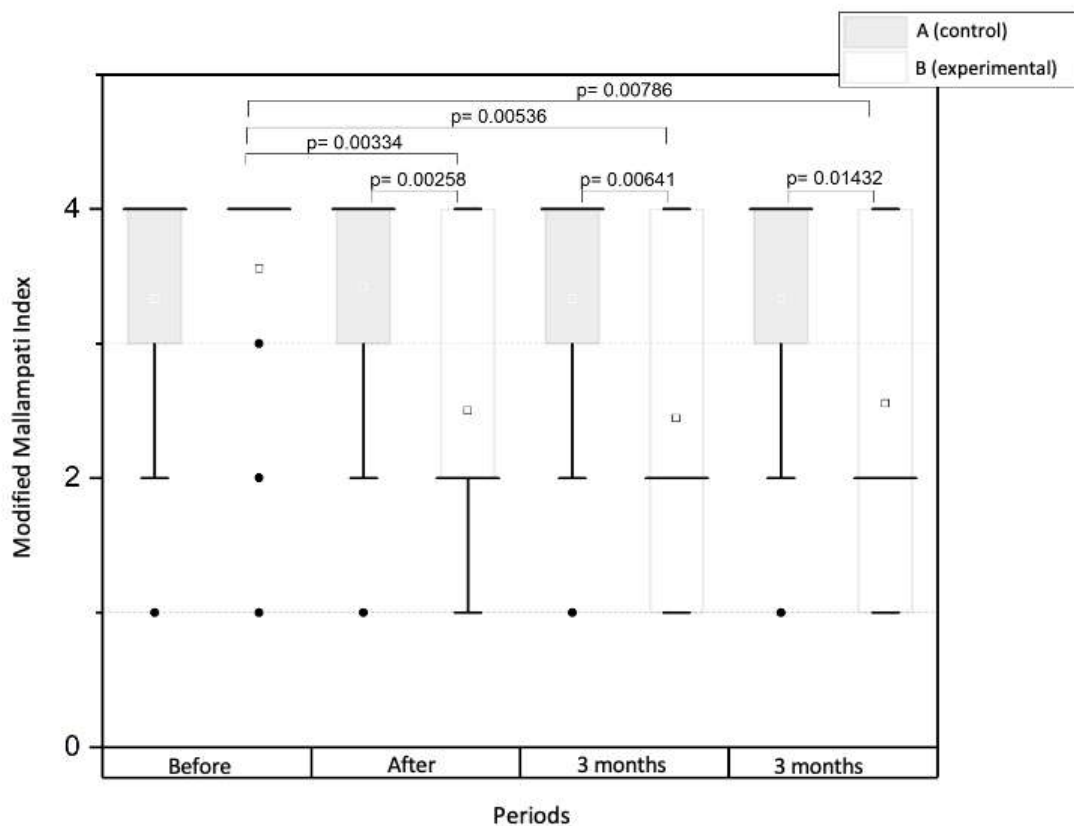

Figure: Modified Mallampati index for each group in each of the analyzed periods.

Oxyhemoglobin Desaturation Index (ODI)

Table – ODI for each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	4.6 ± 8.6	5.9 ± 7.2	3.4 ± 2.8	7.0 ± 7.7	0.42763
B (experiment)	9.2 ± 8.2	4.4 ± 4.3	3.7 ± 4.1	6.9 ± 6.5	0.20934
p (value)	0.42048	0.51162	0.56749	0.79943	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p.
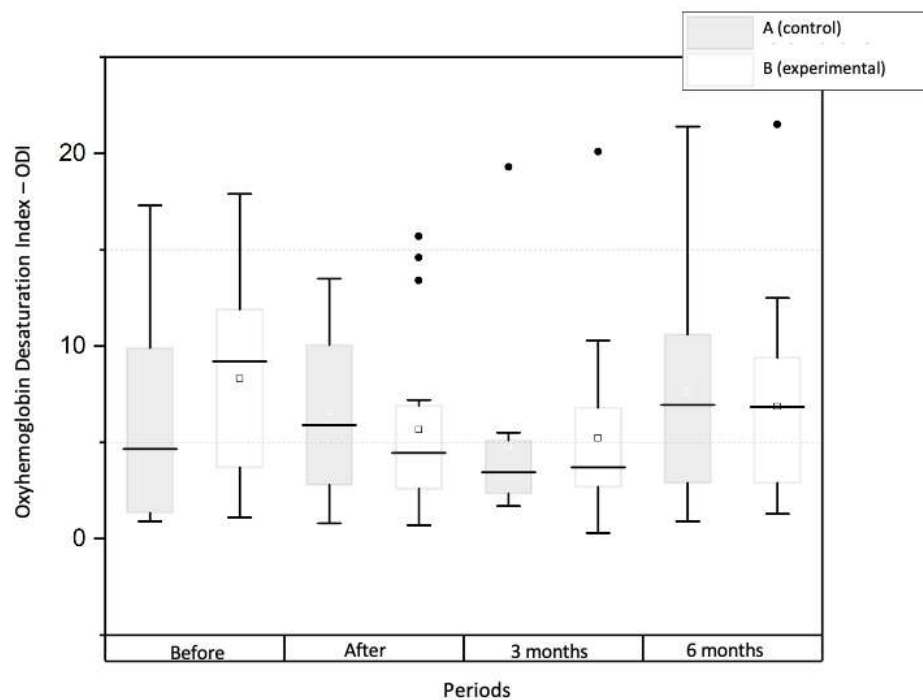
Figure: IDO of each group in each of the analyzed periods.

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Snoring time

Table – Snoring time of each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	11.0 ± 23.5	24.0 ± 22.0	8.0 ± 50.0	37.0 ± 53.0	0.03135
B (experiment)	47.0 ± 29.0	45.0 ± 43.0	25.0 ± 25.0	32.0 ± 47.0	0.00204
p (value)	0.00283	0.15000	0.4308	0.96173	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p. The significance detected in Control group (p= 0.03135) was between the period Before and 6 Months (p= 0.01437). The significance detected in Experiment group (p= 0.00204) was between the period Before and 3 Months (p= 0.00857), between the period After and 3 Months (p= 0.00531) and between the period 3 Months and 6 Months (p= 0.03118).
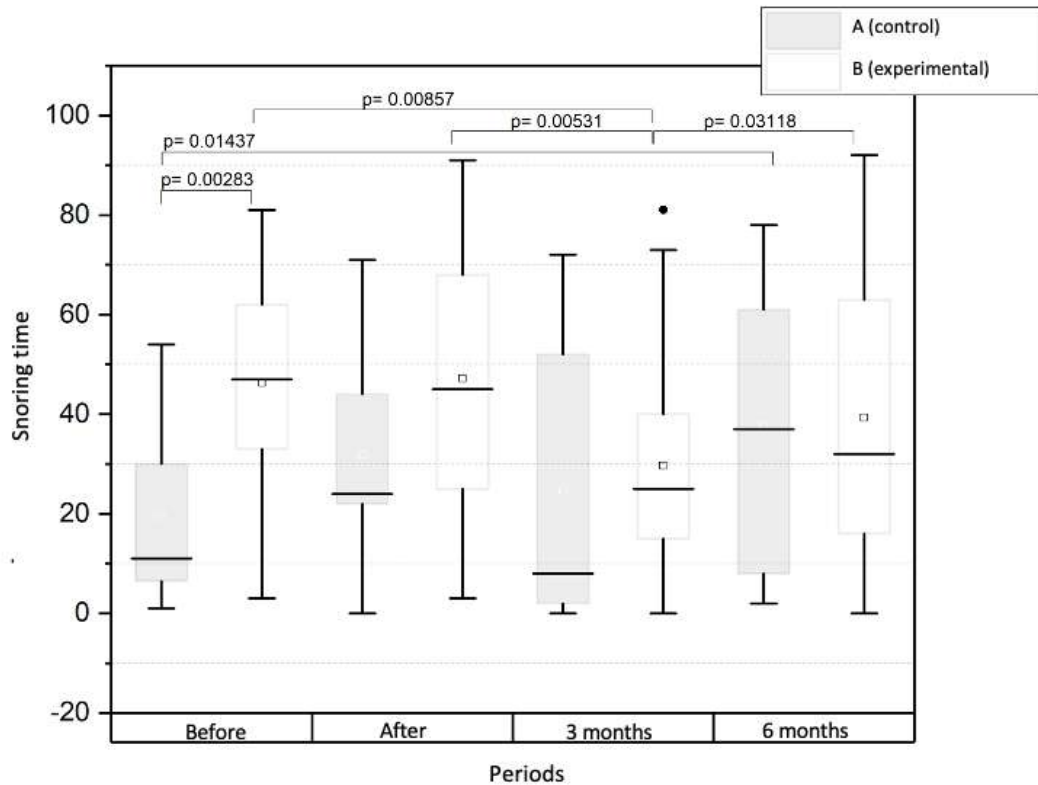

Figure: Snoring time for each group in each of the analyzed periods.

Snoring noise peak amplitude

Table – Snoring noise peak amplitude of each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	41.5 ± 7.4	40.4 ± 11.6	38.0 ± 13.7	40.2 ± 13.9	0.10802
B (experiment)	44.0 ± 10.0	37.8 ± 10.2	35.0 ± 14.5	38.4 ± 7.3	0.00019
p (value)	0.30947	0.47168	0.81569	0.18755	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p. The significance detected in Experiment group (p= 0.00019) was between the period Before and After (p= 0.00109), between the period Before and 3 Months (p= 0.00054), between the period Before and 6 Months (p= 0.00413).
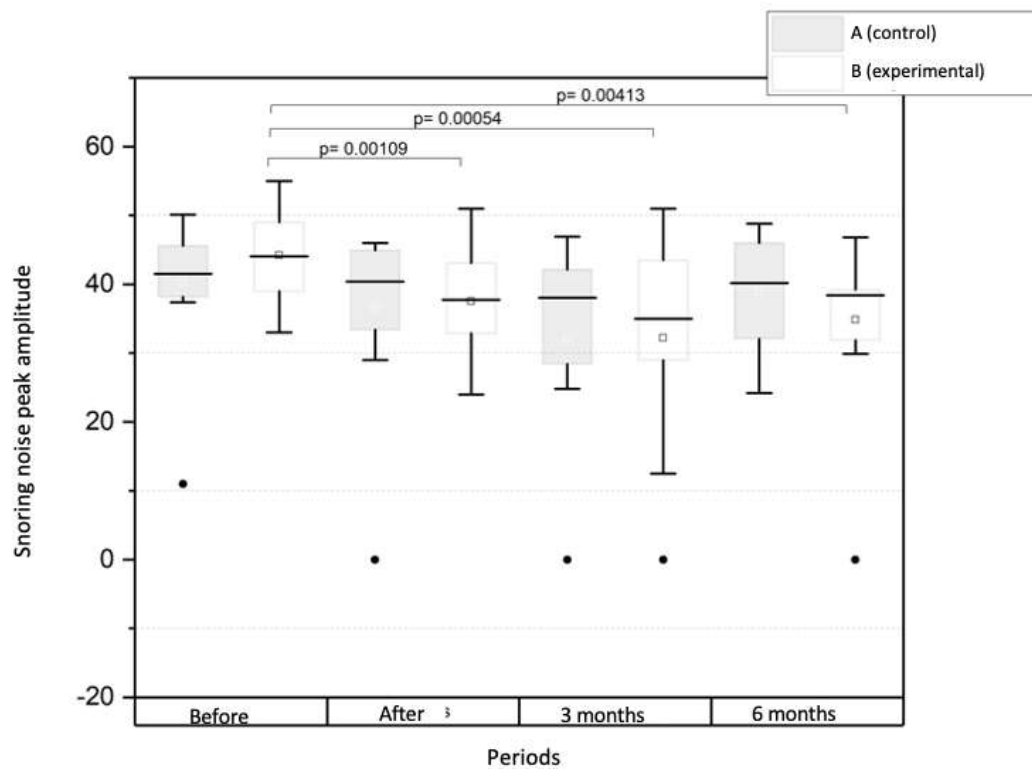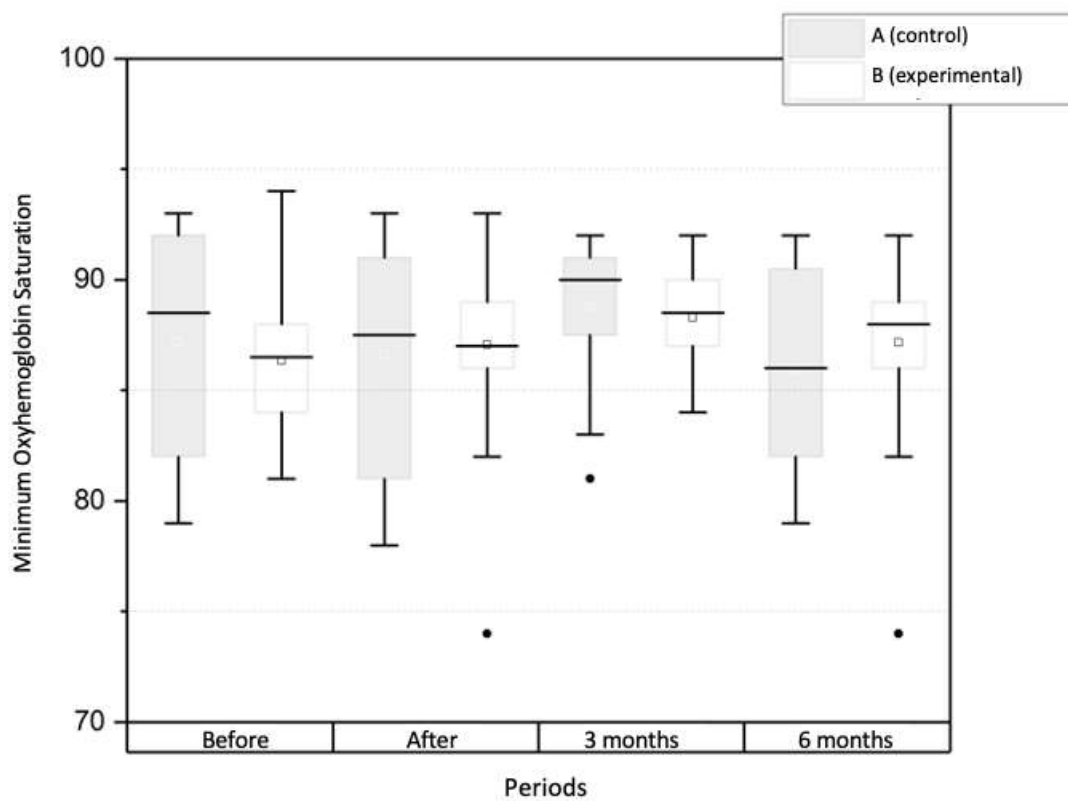

Figure: Peak Amplitude of each group in each of the analyzed periods.

Minimum Oxyhemoglobin Saturation

Table – Minimum oxyhemoglobin saturation during sleep of each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	88.5 ± 10.0	87.5 ± 10.0	90.0 ± 3.5	86.0 ± 8.5	0.42763
B (experiment)	86.5 ± 4.0	87.0 ± 3.0	88.5 ± 3.0	88.0 ± 3.0	0.28976
p (value)	0.45633	0.98303	0.18833	0.52362	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p.

Figure: Minimum oxyhemoglobin saturation of each group in each of the analyzed periods.

Average Oxyhemoglobin Saturation

Table – Average oxyhemoglobin saturation during sleep of each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	95.5 ± 2.5	95.0 ± 1.5	95.0 ± 1.0	95.0 ± 2.0	0.65061
B (experiment)	95.0 ± 2.0	95.0 ± 1.0	95.0 ± 2.0	95.0 ± 1.0	0.74153
p (value)	0.25687	0.34404	0.50788	0.49919	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p.
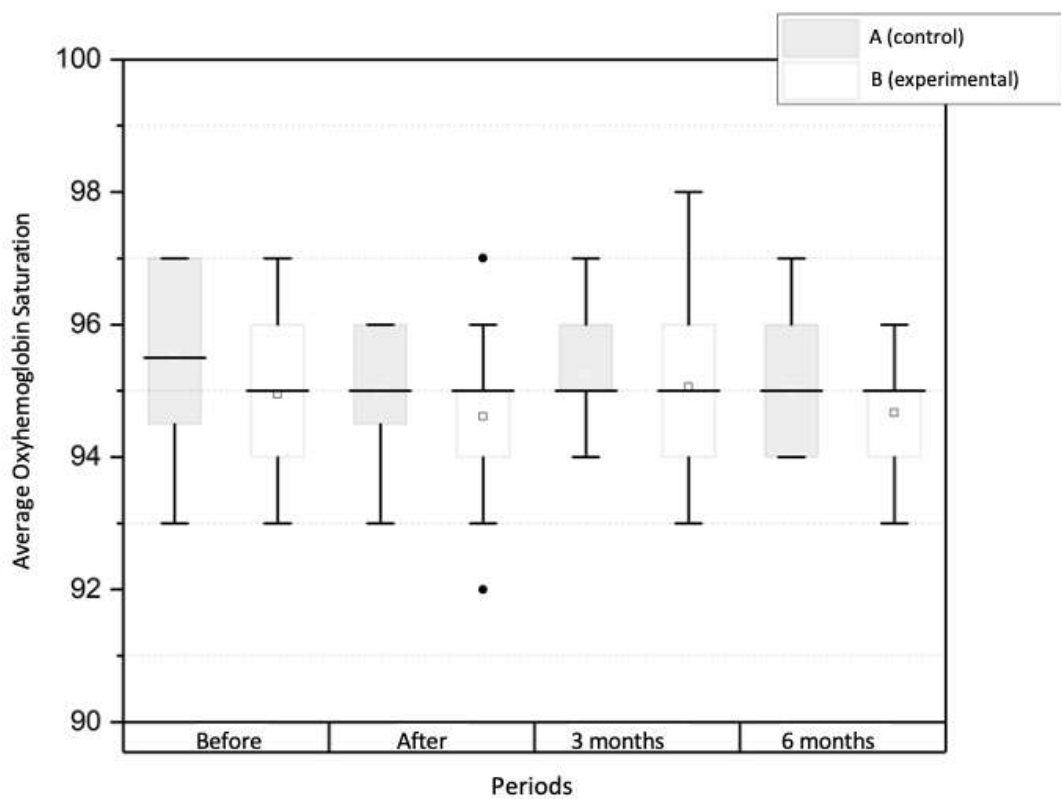

Figure: Mean Oxyhemoglobin Saturation of each group in each of the analyzed periods.

Sleep time with oxyhemoglobin saturation below 90%

Table – Sleep time with oxyhemoglobin saturation below 90% of each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	0.0 ± 1.0	0.0 ± 0.5	0.0 ± 0.0	0.0 ± 1.0	0.47092
B (experiment)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.18321
p (value)	0.6457	0.9999	0.4000	0.0837	

Values represented by median ± interquartile range. The probability the detected difference occurred by chance is the value represented by p.
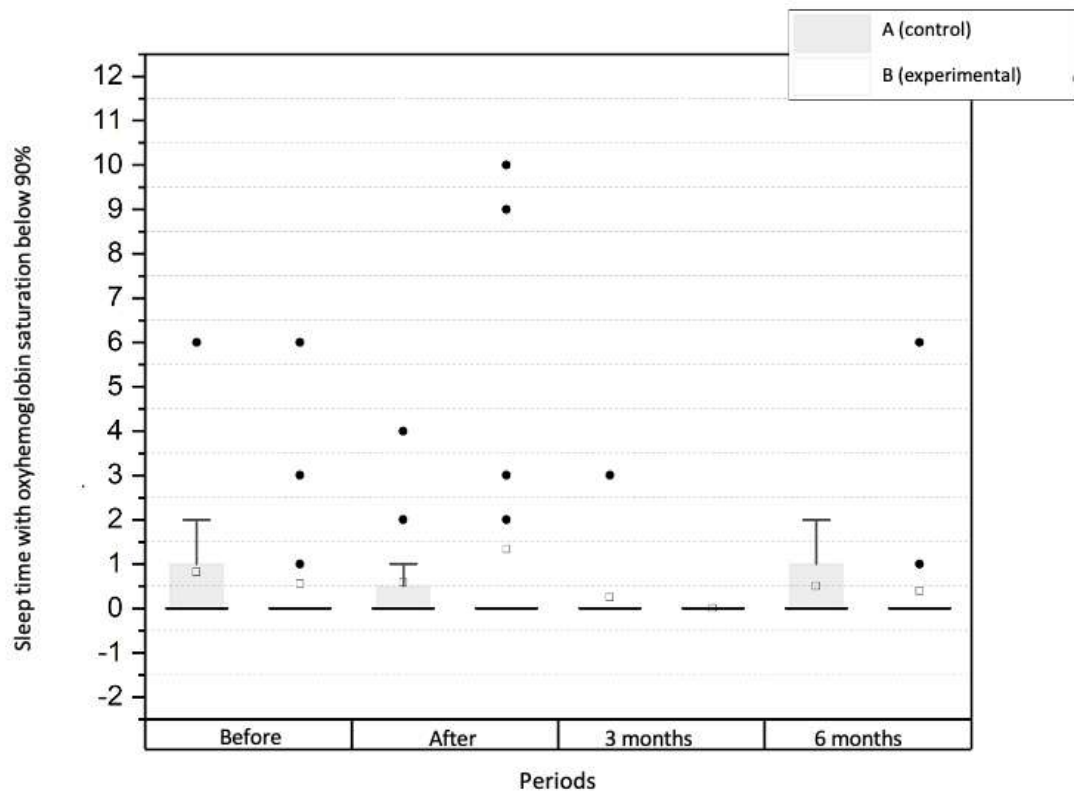

Figure: Sleep time with oxyhemglobin saturation below 90% for each group in each of the analyzed periods.

ESE Questionnaire Score

Table – ESE questionnaire score of each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	8.0 ± 6.5	8.0 ± 6.0	7.0 ± 7.0	7.0 ± 3.0	0.84947
B (experiment)	9.5 ± 7.0	6.5 ± 6.0	3.5 ± 4.0	3.0 ± 1.0	0.00185
p (value)	0.32876	0.79897	0.06495	0.00864	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p. The significance detected in Experiment group (p= 0.00185) was between the period Before and After (p= 0.01100), between the period Before and 3 Months (p= 0.00247), between the period Before and 6 Months (p= 0.03401), between the period After and 3 Months (p= 0.00523) and between the period After and 6 Months (p= 0.03603).
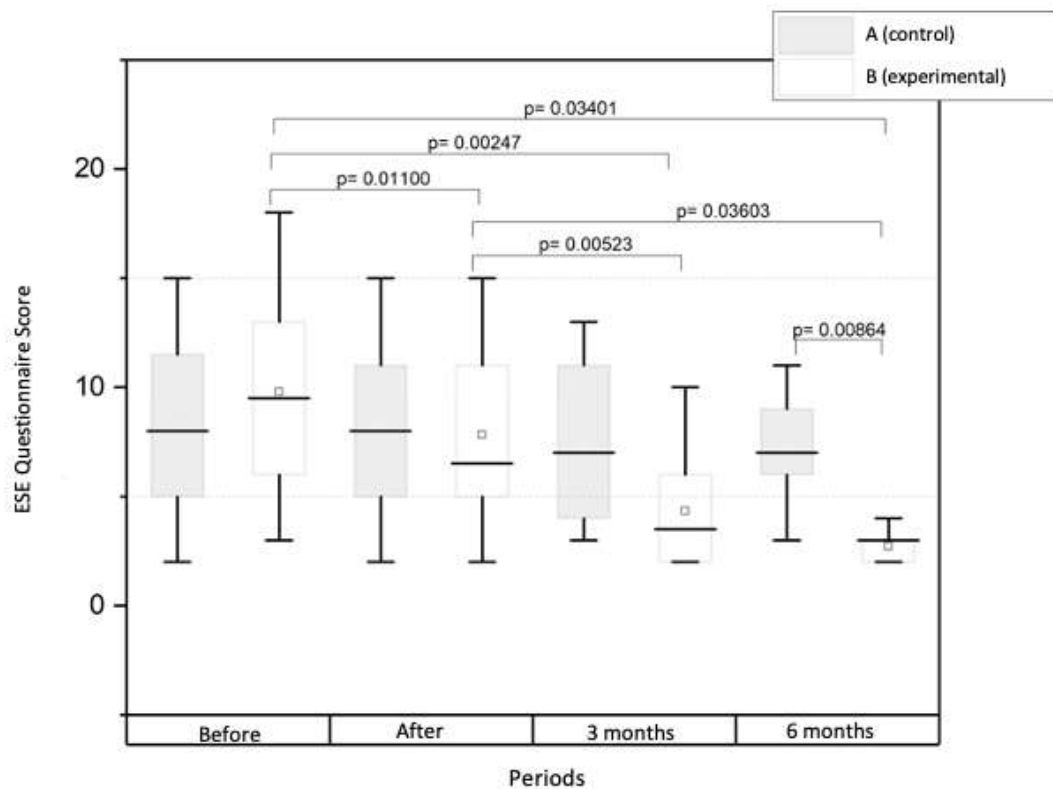

Figure: ESE Questionnaire score of each group in each of the analyzed periods.

PSQI Questionnaire Score

Table – PSQI questionnaire score of each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	4.0 ± 3.5	4.0 ± 2.5	3.0 ± 5.0	3.0 ± 3.0	0.86139
B (experiment)	6.0 ± 3.0	5.0 ± 4.0	4.0 ± 3.5	4.0 ± 4.0	0.03291
p (value)	0.09273	0.14568	0.99999	0.56339	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p. The significance detected in Experiment group (p= 0.03291) was between the period Before and After (p= 0.03651), between the period Before and 3 Months (p= 0.00334) and between the period After and 3 Months (p= 0.00526).
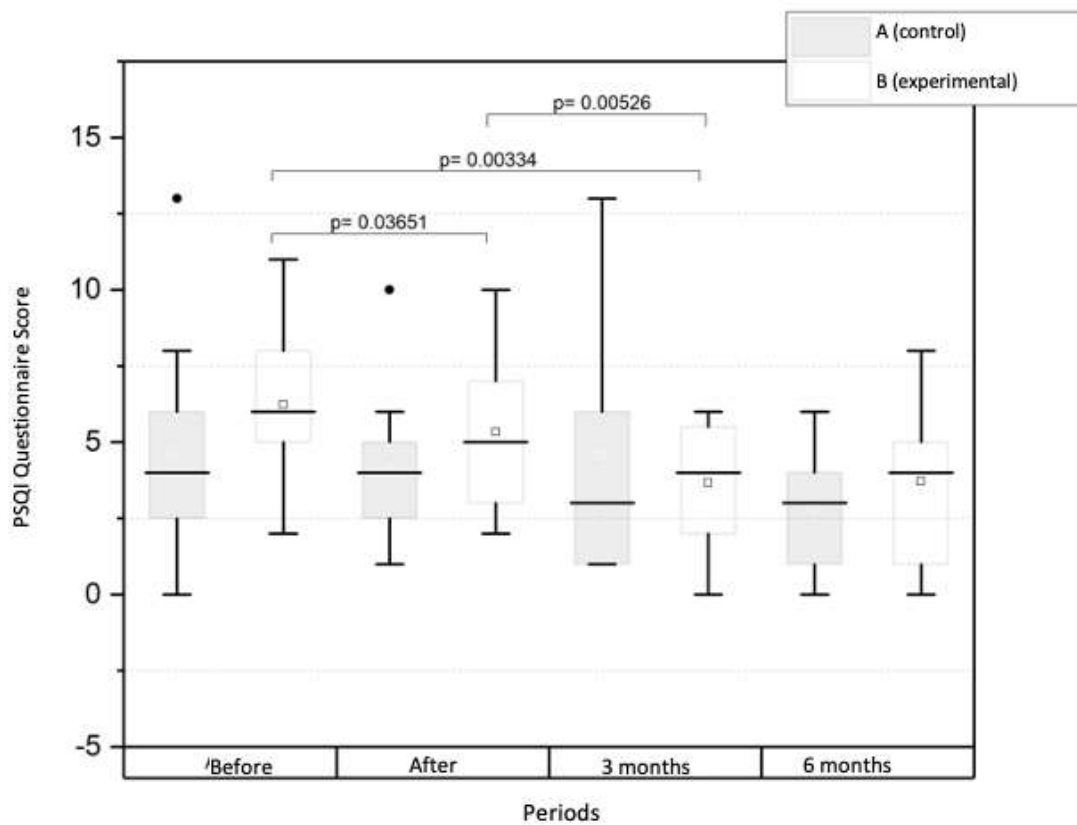

Figure: PSQI Questionnaire score of each group in each of the analyzed periods.

BQ Questionnaire Score

Table – BQ questionnaire score of each group in the different experimental periods.

Groups	Before	After	3 months	6 months	p (value)
A (control)	4.0 ± 1.5	4.5 ± 2.0	5.0 ± 2.0	4.0 ± 2.0	0.77707
B (experiment)	5.0 ± 1.0	5.0 ± 1.0	4.0 ± 2.0	4.0 ± 1.0	0.16462
p (value)	0.0965	0.31221	0.55966	0.70371	

Values represented by median ± interquartile range. Probability the detected difference occurred by chance is the value represented by p.
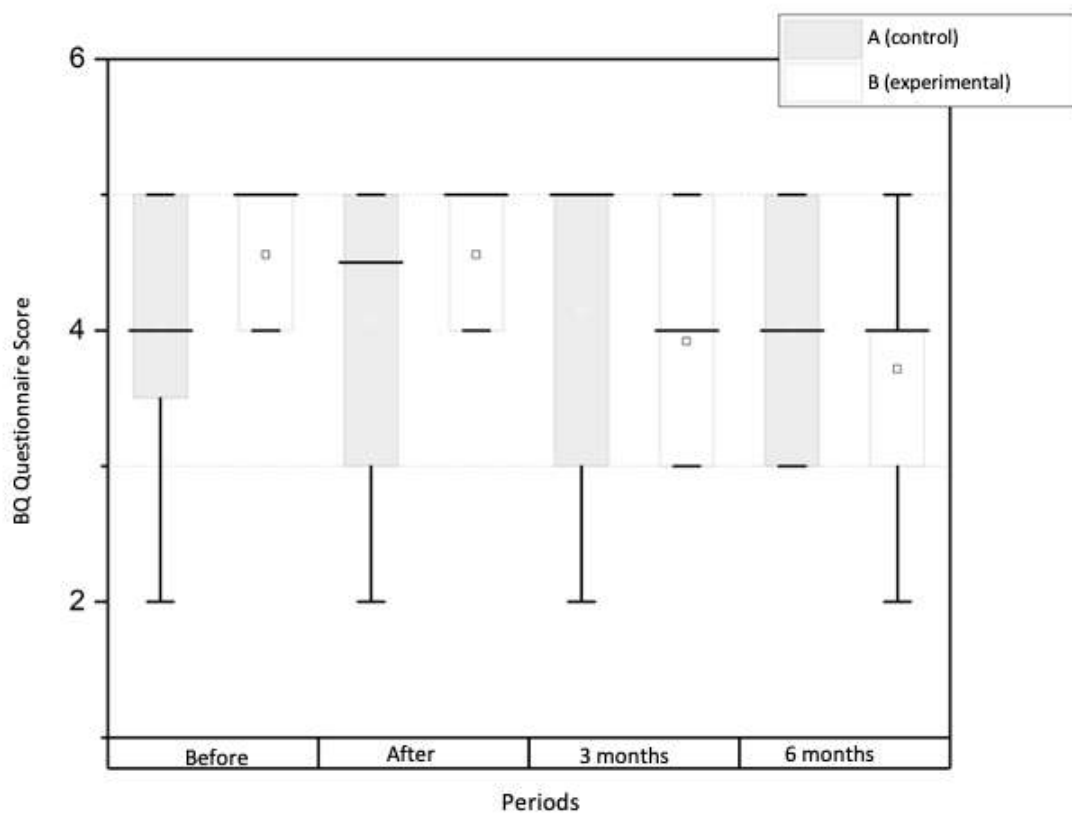

Figure: BQ Questionnaire score of each group in each of the analyzed periods.

INSTITUTO DE PESQUISAS ENERGÉTICAS E NUCLEARES
Diretoria de Pesquisa, Desenvolvimento e Ensino
Av. Prof. Lineu Prestes, 2242 – Cidade Universitária CEP: 05508-000
Fone (11) 2810-1570 ou (11) 2810-1572
SÃO PAULO – São Paulo – Brasil
http://mprofissional.ipen.br