Original Article

Comparison Between Efficacy Of High Level LASER Therapy And Low Level LASER Therapy In Treatment Of Radiation- Induced Oral Mucositis: A Randomized Controlled Trial

Fatma Mohammed Alfeky[1], Heba Mohamed Abd Elshafi [2], Esraa Hany Rostom [3,4], Ehab Saad Abdelnaby[5], Doaa Tammam Atia [6], Shimaa T.Abu El kasem [7,8]

1. Lecturer At Department of Basic Science, Faculty of Physical Therapy, Benha University, Benha, Egypt.
2. Consultant and Head of Physical Therapy Department at Oncology and Nuclear Medicine KASR Al-AINI Hospital, Cairo University, Cairo, Egypt.
3. Assistant Professor at Department of Surgery, Faculty of Physical Therapy, Cairo University, Cairo, Egypt.
4. Assistant Professor at Department of Physical Therapy, Faculty of Medical Rehabilitation Sciences, Medina, Saudi Arabia.
5. Assistant Professor at Department of Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt.
6. Lecturer At Pediatrics Department, Faculty of Physical Therapy, Heliopolis University, Cairo, Egypt.
7. Lecturer At Department of Basic Science, Faculty of Physical Therapy, Galala University, Egypt.
8. Lecturer At Department of Basic Science, Faculty of Physical Therapy, Cairo University, Cairo, Egypt.

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Abstract

Background: Radiation- Induced Oral Mucositis (RIOM) is a frequent debilitating side effect in patients with Head and Neck Cancer (HNC) received Radiotherapy (RT). **Objectives:** to evaluate and compare between the efficacy of High Level LASER Therapy (HLLT) and Low Level LASER Therapy (LLLT) in treatment of RIOM in patients with HNC. **Methods:** Sixty patients of both genders with RIOM were enrolled in the study and distributed randomly into 3 groups: **Study group (A):** 20 patients (8 male and 12 females) were received HLLT by Gallium Arsenide (GA-AS) laser class IV (wavelength 904 nm, average power 3.3W, frequency 1-2000 Hz and energy density 6.04 J/cm^2). Scanning mode was used extraorally all over the oral cavity in one minute for five consecutive days, once a day for 2 weeks. **Study group (B):** 20 patients (6 male and 14 females) were received LLLT GA-AS laser class 3B with a small hand held probe intraorally both in ulcerated and erythematous areas (wavelength 904 nm, average power 70.5mW and energy density 5 J/cm^2 for one minute on each point) for five consecutive days, once a day for 2 weeks. **Control group (C):** 20 patients (9 males and 11 females) were received shame LASER**.** All patients in the 3 groups were received routine medical care in the form of local antifungal, analgesics and mouth wash**. Outcome measures:** Patients were evaluated for OM severity according to World Health Organization (WHO) grading scale. Pain intensity was assessed by visual analogue scale (VAS). Assessment of the dependent variables was performed at two occasions: first at baseline, second after two weeks (ten LASER sessions). **Results**: Within group analysis, there were statistically significant difference between pre and post treatment at all variables in both study groups A and B in favor to group A ($p<0.05$) but there were no statistical significant difference at control group (C) variables. Between groups analysis at post-treatment revealed that there were statistical significant difference in all measured variables between three group as $p<0.05$. **Conclusion**: HLLT has a superior effect in reduction of pain and severity of RIOM compared to LLLT in patients with RIOM.

Keywords: Head and Neck Cancer; High Level LASER Therapy; Low Level LASER Therapy; Radiation- Induced Oral Mucositis

INTRODUCTION

Head and neck cancer (HNC) is a frequent neoplasm type including the otolaryngology, oral-maxillofacial and neck tumors. Recently, Radiotherapy (RT) has become popular as a treatment option for HNC patients including intensity modulated RT, particle therapy, stereotactic body radiation therapy and high dose rate brachytherapy **(1)**.

Oral mucositis (OM) is an inflammatory disorder of the oral cavity mucosa. It is characterized by erythema, ulceration, bleeding, edema, and pain. It impairs oral functions as nutrition, prolongs hospital stay, increases financial burden and increases the risk of systemic spread of infection. OM significantly impacts health care cost, quality of life (QoL) and treatment outcome **(2-5).**

OM prevalence is 22.3% in advanced cancer patients, 100% of those treated by RT, 90% of those received hematopoietic stem cell transplantation (HSCT) and 40% of those who received chemotherapy (CT) **(6-8).** So, Radiation-induced oral mucositis (RIOM) is a frequent side effect in patients with HNC undergoing RT due to radiation-induced disturbance of basal cells of the epithelium of the oral surface rather than superficial cells direct damage **(9).**

RIOM can persist for weeks with average 2 to 3 weeks and it could persist longer in severe neutropenia but CT related to OM can resolve within a few days after completion of CT **(10-12).** Thus, it is essential to pay attention to RIOM therapeutic interventions.

OM pathophysiology composed of five biological stages. First stage is the beginning of oral mucosal injury after RT or CT. Second stage is a primary injury from reactive oxygen species (ROS) production. Third stage is the damage amplification after host inflammatory response by increase in the production of substance P and bradykinin, release of histamine, increase cyclo-oxygenase formation of prostaglandin E2 and upregulation of interleukin 6 and nuclear factor kappa B. Forth stage is ulceration of the mucosa caused by epithelial necrosis and apoptosis. Fifth stage is healing by cell proliferation and angiogenesis. RIOM treatment is directed at complications and symptoms **(13).**

Low level laser therapy (LLLT) is defined by the North American Association for Laser Therapy and World Association for Laser Therapy conference in 2014 as the therapeutic utilization of light uptake by endogenous chromophores which trigger non-thermal biological reactions through photophysical and photochemical processes causing a physiological alteration **(14).** LLLT reduces pain and inflammation. It also enhances wound repair by promotion of different stages of tissue healing: inflammatory phase, the proliferative phase and the remodeling phase through immunomodulation, synthesis of collagen by fibroblasts, myofibroblast differentiation and angiogenesis **(14,15-17)**

High level laser therapy (HLLT) is the treatment by class IV laser. It has photochemical and photothermal effects in the deep tissues. It induces the generation of ATP and mitochondrial oxidation by delivering high amount of energy output inside tissues. HILT causes rapid edema absorption and removes exudates through increased blood flow and metabolism **(18).**

Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC and ISOO) updated guidelines for management of RIOM and associated pain in 2020 by basic oral care, antimicrobials, mucosal coating agents, growth factors, anti-inflammatory, analgesics, anesthetics, cytokines and

cryotherapy. They recommended LLLT intraoral approach for prevention in HNC undergoing RT (with or without CT) and HSCT **(19).**

Currently, there is no evidence based guideline for the OM treatment with LLLT and its related pain. The guidelines are for the LLLT role in OM prevention with about 9 times more effective than the non-application of LLLT **(20,21).** In literature, many studies revealed that LLLT is effective in OM prevention by reduction of incidence, severity and related pain in RT, CT and HSCT patients. Some studies reported its efficacy specific for RIOM **(7,20,22-27)**. Therefore, LLLT can be regarded necessary medically in OM prevention.

Up to our knowledge, no study in literature investigated effect of HLLT in the treatment of RIOM and compared between LLLT and HLLLT in human. There is only a study on effect of HLLT in OM treatment in mouse received CT **(28),** a study on HLLT effect on pediatric OM patients undergoing HSCT and CT **(29)** and a study in the role of HLLT in OM treatment for Onco-haematological pediatric patients received CT **(30).** Also, there is a study comparing between intra-oral and extra-oral diode LASER in the treatment of CT induced OM in rats **(31),** a study comparing between Intra-oral and extra-oral photobiomodulation (PBM) therapy in the prevention of OM in patients with HSCT **(32),** a study comparing between LLLT, LED, and HLLT in OM treatment in hamsters received CT **(33),** and study comparing between prophylactic LLLT and HLLT with different protocols in the prevention of RIOM **(34).**

The role of LLLT as a curative treatment for RIOM still lacks strong evidence and the role of HLLT in the treatment of RIOM has not been illustrated clearly yet. Thus, the aim of the study is to evaluate and compare between efficacy of HLLT and LLLT in RIOM treatment in HNC patients.

Subjects, Materials and Methods

Design of the study:

A randomized controlled clinical trial was carried out in accordance with the Helsinki Declaration **(35)** and the Consolidated Standards of Reporting Trials guidelines. The study was conducted at the centre of Clinical Oncology and Nuclear Medicine in Kasr Elaini hospital, Cairo, Egypt. The protocol was prospectively approved by Faculty of Physical Therapy's Research Ethics Committee, Cairo University, Egypt (**NO:P.T.REC/012/004147**).

Subjects and randomization:

Sixty patients diagnosed with RIOM (grade I, II and III) were participated in the study. They were referred from the clinical oncologist to the Physical Therapy Department at Kasr Elaini hospital, Cairo, Egypt. The patients assigned randomly by opaque sealed envelopes into 3 groups: **Study group (A):** 20 patients (8 male and 12 females) were received HLLT, **Study group (B):** 20 patients (6 male and 14 females) were received LLLT and **Control group (C):** 20 patients (9 males and 11 females) were received shame LASER.

The patients enrolled in the study if they met the inclusion criteria; age 18 years or older, both sexes and RT after surgical excisional head and neck squamous cell carcinoma. Patients were excluded if they have grade 4 RIOM, received chemotherapy concomitant to RT or four weeks before the study, HSCT, current smokers, distant metastasis, pregnancy, breastfeeding, sever collagen vascular disease and any uncontrolled comorbidities such as pulmonary, kidney, liver, or heart failure. All patients were given written informed consent.

Calculation of Sample Size

Sample size was calculated using the F-test (MANOVA), with a power of 80% and a type I error of 5%. The effect size (0.42) was computed based on the primary outcome (VAS) from a 15-subject pilot study .The minimal sample size was 45, and the number was increased by 10% to accommodate for drop outs. The proper

sample size was 60 subjects. For the calculations, G* Power version 3.1.9.2 (Franz Faul, Uni Kiel, Germany) was utilized.

Assessment:

Assessment of dependent variables was performed at two occasions; first at baseline, second after two weeks (ten LASER sessions).

1. OM severity assessment

OM severity was evaluated by the World Health Organization (WHO) grading scale. WHO is an objective and measurable scale to measure the severity of OM **(36).** Evaluation was performed by a blinded examiner who did not administer LASER. The WHO scale combines pain, clinical and dietary variables taking into account individual's tolerance of oral consumption of solids and liquids remains critical for OM morbidity. Oral mucositis was classified in four grades according to WHO as follows: Grade 0 (absence of signs and symptoms), Grade I (presence of erythema with oral pain), Grade II (presence of ulcers, erythema, liquid and solid food tolerated), Grade III (ulcers and only liquid feeding) and Grade IV (unable to feed orally) **(15).**

2. Pain intensity

Pain associated with OM was assessed by the visual analogue scale (VAS). VAS is a valid and reliable method for assessment of pain intensity. VAS measures self-reported intensity of pain by using a numerical value; 0 indicates the pain absence and 10 indicates the maximum score **(37).**

Intervention:

All the patients in the 3 groups were received routine medical care in the form of local antifungal, analgesics and mouth wash prescribed by the physician concurrent to the laser therapy. They also received same instructions about oral hygiene and abstinence from tobacco and alcohol. Professional and the patient required to wear safety goggles to prevent eye injury during LASER application.

a. Patients in study group (A) received HLLT: HLLT was provided by (M6 Robotized) Gallium Arsenide (GA-AS) laser class IV, wave length 904 nm. The parameters employed were the following: average power 3.3 W, frequency 1-2000 Hz and energy density 6.04 J/cm^2. Laser application was performed in a rotatory motion extra orally all over the oral cavity using scanning mode in one minute. HLLT was performed once a day for five consecutive days.

b. Patients in study group (B) received LLLT: LLLT was performed using Pulsed GA-As class 3B (Phyaction CL-904) manufactured by Uniphy technology and made in Belgium containing small hand held probe. The equipment provides pulsed Ga-As LASER, with wave length 904 nm. The parameters employed were the following: pulse peak power 13.5W, frequency 2-30,000 Hz, and average power 70,5mW. Energy density used was 5 J/cm^2 as an optimum dose agreed in the 2018 WALT meeting. Intra-oral technique was applied on the oral cavity in erythematous and ulcerated areas one minute on each point once a day for five consecutive days. Before each session, calibration of the laser equipment was carried out in accordance with the specifications given by the manufacturer's handbook. A disposable plastic film (small, flexible, transparent film) was placed on the head of the

laser probe and replaced before each session for each patient. Before and after laser therapy, photos of the oral cavity were obtained **(38-40).**

c. Patients in control group (C) received Sham LLLT: LASER wasn't turned on and only the hand piece was used.

Statistical analysis:

All data were found to be normally distributed except sex (Shapiro-Wilk test). For analysis of demographic data, One-way analysis of variance (ANOVA) was performed. Different in sex between groups was performed by Chi square (X2) test. Mixed multivariate analysis of variance (MANOVA) was performed to determine the treatment's effect and the interaction between time and treatment. The Bonferroni test was performed when there were significant differences between groups. The differences between groups were measured using the partial eta square (η^2). SPSS version 23 (IBM Corp., New York, USA) was used for data analysis.

Results:

Demographic data: ANOVA test revealed that there was no difference between patients in three groups regarding age, weight, height also Chi square test found no differences between groups in sex **(Table 1).**

Table 1: Demographic data

	Mean ± SD			**F value**	**p-value**
	HLLT Group	LLLT Group	Control group		
Age: (years)	49.65±6.77	51.75±6.18	49.20±6.70	0.851	0.428 [b]
Weight: (kg)	75.55±5.91	73.15±6.08	74.60±7.05	0.720	0.491 [b]
Height: (cm)	167.05±5.34	169.45±6.33	168.55±6.01	0.841	0.4 [b]
Sex distribution					
Males	8(40%)	6 (30%)	9 (45%)		X^2=0.98
Females	12 (60%)	14 (70%)	11 (55%)		P=0.61 [b]

[b]: no significance difference; SD: standard deviation; p-value: significance level; X^2; chi square test.

As a general mixed MANOVA revealed a statistically significant difference between groups as Wilks' Lambda (ʎ) = 0.508, f=11.27, p=0.0001 and η^2=0.287. Moreover, there were significant difference at time as ʎ = 0.074, f= 351.6, p=0.0001 and η^2 = 0.926. Also, there were significant interaction between group and time as ʎ = 0.121, f = 52.33, p=0.0001 and η^2 =0.651.

Multiple pairwise comparisons by the Bonferroni correction reported that statistically significant differences between pre and post-treatment for VAS and WHO scale in the HLLT group and LLLT group compared to control group, with more improvement in HLLT group as the percentage of reduction in pain intensity and WHO scale were 62% and 55.7% respectively while the percentage of reduction in LLLT group were 29% and 30.9% respectively.

Boferronie also found no significant differences between groups before treatment, but significant differences between both LLLT group and control group compared to LLLT group after treatment **(Table 2)**

Table 2: within and between group analysis

Variables	HLLT group (A)	LLLT group (B)	Control Group (C)	p-value between	f-value between	η^2
WHO scale		**Mean ±SD**				
Pre-treatment	2.6±0.50	2.1±0.78	2.2±0.76	A Vs. B=.08 ** A Vs. C=0.226** B Vs. C=1.00**	2.87	**0.065**
Post-treatment	1.15±0.36	1.45±0.60	2.05±0.75	A Vs. B =0.35** A Vs. C=0.0001* B Vs. C=0.007**	11.70	**0.291**
p-value (within)	0.0001 *	0.0001 *	0.238 **			
% of change	-55.7%	-30.9%	-6.8%			
MD	1.45	0.65	0.15			
95% CI	1.19 to 1.70	0.39 to 0.90	-0.10 to 0.40			
VAS (pain intensity)		**Mean ±SD**				
Pre-treatment	7.5±1.05	7.4±1.04	7.3±1.03	1.00**	0.061	**0.002**
Post-treatment	2.85±0.74	5.25±1.25	7.15±0.81	0.0001*	100.15	**0.778**
p-value	0.0001 *	0.0001 *	0.146 **			
%of change	-62%	-29%	-2%			
MD	4.65	2.15	0.15			
95% CI	4.31 to 4.99	1.81 to 2.49	-0.090 to 0.59			

**: no significance difference; *: significant difference; SD: standard deviation; p-value: significance level; VAS: visual analogue scale; WHO scale; CI: confidence interval; MD: mean difference; η^2: Partial Eta Square.

Discussion

RIOM is associated with increased morbidity and mortality and considered as a debilitating adverse effect of RT in HNC patients. Thus, it needs a multidisciplinary team to treat it and improve QoL. The purpose of the present study is to evaluate and compare efficacy of HLLT and LLLT in RIOM treatment in patients with HNC. According to the current study's data analysis, there were significant improvement in Pain RIOM and pain level in both study groups A and B compared to control group, with more improvement in HLLT group (A) as the percentage of reduction in pain intensity and WHO scale were 62% and 55.7%, respectively while the percentage of reduction LLLT (B) were 29% and 30.9%, respectively.

Regarding the reduction of severity of RIOM with LLLT, the findings of the present study are similar to the systematic review and meta-analysis study of **Anschau et al. (41).** They assessed the effect of LLLT in the OM treatment and found that LLLLT has moderate evidence of effectiveness in OM healing in adult patients receiving cancer therapy as the OM resolution time potentially reduced by approximately 4.21 days. In children, no enough evidence on LLLT effectiveness in OM treatment **(41).** Also, the results of the present study are in accordance with **Zanin et al. (42)**. They evaluated the 660-nm diode laser on 70 individuals with OM undergoing RT and CT in 7 weeks and found that LLLT is effective in OM prevention and treatment providing more comfort and a better QoL **(42)**. Moreover, the findings of the present study are in agreement with studies in the literature that revealed the effectiveness of LLLT in OM severity as in the study of Oton-**Leite et al. (43)** who reported that LLLT has OM

improvement in patients with HNC undergoing CT/RT that reduces inflammation and stimulates OM repair. Also, **Fekrazad and Chiniforush (44)** and **Gautam et al. (45)** reported that LLLT is effective in OM as it improves QoL and patient's subjective experience in patients with HNC undergoing CT/RT.

Regarding the reduction of pain and severity of RIOM with LLLT, the findings of the present study are in accordance with **Campos et al. (33)** who reported that LLLT reduces pain and stimulates the salivary glands. Also, LLLT prevents and treats OM. Also, **Peng et al. (46)** conducted a systematic review and meta-analysis in the prevention and treatment of oral mucositis (OM) in 1616 participants receiving CT and RT in 2020. Thirty studies were analyzed (26 studies investigated prophylactic LLLT and 6 studies assessed therapeutic LLLT). They reported that prophylactic LLLT is effective in OM prevention as it reduced the overall mean OM grade, pain mean score, severe pain overall incidence and severe OM incidence. Therapeutic LLLT has significant reduction of severe OM duration by 5.81 days ($P < .01$) but did not significantly decrease patients' number with severe OM after 7-day treatment ($P= 0.14$) compared to the control group **(46)**. Additionally, **Carvalho et al. (47)** reported that LLLT reduces OM intensity and associated pain. Furthermore, **Gautam et al.** (**22**) conducted a study on effect of LLLT in elderly patients with RIOM in HNC. They reported that LLLT reduces pain and OM severity and duration. Also, LLLT reduces the total parenteral nutrition, opioid analgesics need and radiation breaks **(22)**. Also, **Scully et al. (48)** found that LLLT decreased the severity of OM and its associated pain.

Contradicting to present study results regarding the effect of LLLT on pain reduction, **Soares et al. (49)** and **Gautam et al. (50)** reported no significant pain reduction, but a significant reduction of analgesics use.

Concerning the safety of LLLT, **Redman et al. (51)** and **Sandoval et al. (52)** found that LLLT is a safe well-tolerated therapy that reduces OM severity and associated pain in children and adults.

LLLT has a significant impact on cellular activity. To induce biological processes in the tissues, cells must be supplied by a biphasic dose. Biphasic dose means the optimal light dose in any specific application. Lower levels of light induce photobiostimulation. Higher levels of light produce Photo-induced cellular inhibition **(53-55).**

Regarding the improvement in RIOM severity by LLLT in the current study, it may be due to stimulation of metabolic, photophysical and photochemical processes. Chromophores in respiratory chain of mitochondria absorb Laser with ATP increase that increases cellular proliferation and protein synthesis of IL-6, IL-8 and TNF-α that assists RIOM healing **(56).**

Regarding the reduction of pain in RIOM by LLLT, it may be due to stimulation of peripheral nerve, cellular membrane hyperpolarization alteration and ATP production which preserves the membrane's stability and promotes the threshold of pain **(57).** Also, LLLT could facilitate peripheral endogenous opioid production **(58)** and reduces serum prostaglandin E2 **(59).**

Regarding the superior effect of HLLT compared to LLLT in reduction of pain and RIOM severity shown in the current study results, it is in accordance with results obtained from **Ottaviani et al (28)** who studied the effect of HLLT on CT-induced OM in mouse model with different parameters (970 nm diode laser, continuous 2.5 MW, Duty cycle 50% at 5 W, 30 seconds, 0.5 cm spot size diameter and 375 J/cm^2. They reported that HLLT is more effective than LLLT in OM healing, inflammation reduction, tissue integrity maintains ace and new arterioles formation of inside the granulation tissue **(28).** Moreover, **Thieme et al., (31)** conducted a study on treatment of OM induced by CT in rats and concluded that intra-oral diode LLLT and extr-aoral diode HLLT reduced OM, enhanced biostimulation without cytotoxicity, demonstrated positive results on the histopathological, clinical, and redox state in OM induced by 5-FU but HLLT targets deeper tissues, reduces inflammation and improves healing more than LLLT **(31).**

In contrast to the present study findings regarding the superior effect of HLLT compared to LLLT in reduction of pain and RIOM severity, **Ramos-Pinto et al., (32)** conducted a randomized trial comparing between Intraoral and extra-oral PBM therapy in the prevention of OM in patients with HSCT and they concluded that both extra-oral PBM utilizing HLLT and intr-aoral PBM using LLLT showed similar results but extra-oral PBM utilizing HLLT reduced LASER application session time by 4 minutes **(32).** As well as, **Campos et al. (33)** compaired LLLT, LED and HLLT in treatment of OM hamsters undergoing CT with the following parameters (808 nm, defocused mode, 400 μm optical fiber, one W/cm^2, 1.0-W continuous wave mode,10 seconds in scanning motion).

They reported that LLLT and LED therapies produce better results than HLLT **(33).** The possible justification of contradiction may be due to different parameters.

Simões et al., (43) conducted a study on 39 HNC patients to prevent RIOM with prophylactic LLLT and HLLT with different protocols. They reported that using LLLT alone or in conjunction with HLLT if administered 3 times per week maintains RIOM grade at I or II and prevents an increase in the nociceptive reaction. Also combination of LLLT with HLLT is more effective in reduction of pain but delays the time of healing.

Regarding safety and reduction of pain by HLLT, the findings of the present study are in same line with **Vitale et al. (29).** They studied the effect of HLLT in 16 pediatric OM patients undergoing HSCT and CT in 11days and conclude that HPLT is non-invasive safe therapy reduces hospitalization necessity and parenteral diet and improves QoL. Also, HLLT has a statistically significant reduction of pain 3 days after the first LASER session and complete repair and pain reduction were achieved on day 11 **(29).** Also, **Chermetz et al. (30)** conducted HLLT in the treatment of 18 onco-haematological paediatric patients with OM received CT in 11 days and reported that HLLT is a safe, non-invasive and potentially effective in Onco-haematological paediatric patients.

Regarding the superior effect of HLLT compared to LLLT in reduction of RIOM severity shown in the current study results, it may be due to photothermal and photochemical effects of HLLT. It increases in temperature of superficial tissue rapidly and compared to LLLT, HLLT transmits energy deeper beyond. HLLT stimulates new arterioles formation to repair the mucosal layer. Also, It also has direct effects on smooth muscle cells to stimulate proliferation and metabolism. Then, the newly formed vessels in the granulation tissue create a structural and functional maturation to be impermeable and to maintain an increased circulation which enhances the healing process **(18,60,61).**

Regarding the superior effect of HLLT compared to LLLT in reduction of pain shown in the current study results, it may be due to endogenous opioids secretion as beta endorphins which block pain in central nervous system. Also, HLLT decreases substance P production by peripheral receptors. Moreover, HLLT increases the latency and decreases sensory nerves conduction velocity by inhibiting A-delta and C-fiber transmission which reduces the transmission of pain signals. Also, HLLT decreases histamine and bradykinin in tissues and increases the pain threshold **(62-65).**

Regarding GA-AS laser used in the current study, it has deep effect as wavelengths between 780 and 950 nm penetrate deeper but shorter wavelengths between 633 and 700 nm only reach the superficial layers **(14).**

In the current study, HLLT was delivered through LASER Scanner extra-orally. This offers many advantages related to convenience of use, treatment of large areas in limited amount of time (one minute only) without cossidering the number of points and lower risk of infection compared with LLLT which delivered intra-orally that may cause oral discomfort and makes LLLT more complicated and limited in application especially in the presence of OM grade more than 2. Based on the results of the current study, it is recommended using HLLT as a novel, more efficient and effective approach in the treatment of RIOM to reduce pain and OM severity.

Study limitations:

Lack of follow-up makes a difficulty in determining how long changes might last in the subjects. Also, small sample size may affect the results. Yet, a power test was carried out to determine the least appropriate number of subjects.

Conclusion:

HLLT has a superior effect in reduction of pain and severity of RIOM compared to LLLT in patients with RIOM.

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Conflict of interest

The authors declare that no conflict of interest

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