



Effect of Light-Emitting Diode Phototherapy on Allograft Bone After Open Sinus Lift Surgery: A Randomized Clinical Trial (Concurrent Parallel)

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Abstract

Introduction: Phototherapy with a light-emitting diode (LED) is used in medicine due to its potential bio-stimulatory effects on the human body. However, controversy still exists regarding the efficacy of low-level laser therapy (LLLT) and phototherapy with LED. This in vivo study aimed to quantitatively and qualitatively assess the newly formed bone following LED phototherapy of the human maxillary sinuses.

Methods: This randomized clinical trial (concurrent parallel) was conducted on 44 patients in two groups (n=22) at the Implant Department of Tehran University of Medical Sciences. Randomization was done by a random sequence generator program. The inclusion criteria were absence of chronic sinusitis and chronic bone marrow conditions, no history of surgery at the site, absence of diabetes mellitus, no history of chemotherapy or radiotherapy, maxillary premolar edentulism, and signing informed consent forms. Group A underwent LED phototherapy with 620 ± 2 nm wavelength for 20 minutes daily for a total of 21 days after sinus lift surgery. Group B served as the control group and did not receive phototherapy. After 6 months, the grafted sites were re-opened for implant placement, and bone biopsy samples were obtained using a trephine bur. The samples were stained with hematoxylin and eosin and inspected under a light microscope. The results were statistically analyzed using the Mann-Whitney U test. Both the surgeon and pathologist were blinded to the group allocation of patients.

Results: Forty tissue specimens were analyzed. Insignificant differences existed between the two groups in terms of the degree of inflammation, bone quality, and maturity of collagen. Histological analyses revealed no significant difference in the mineralized areas of bone between the two groups ($P>0.05$).

Conclusion: The results indicated that LED phototherapy cannot significantly enhance osteogenesis after sinus lift surgery. No side effects were observed in the experimental group.

Keywords: Laser phototherapy; Low-level light therapy; Phototherapy, Biostimulation, Laser.



Introduction

The alveolar bone undergoes some changes following tooth loss. The edentulous alveolar socket collapses in the process of healing. This collapse results in the loss of height and width of the alveolar bone. Moreover, following the loss of maxillary premolars and molars, the maxillary sinus floor also collapses as much as the underlying bone thickness allows. This results in a reduction of the

available bone volume for implant placement. In the sinus lift procedure, a bone graft is placed in the maxillary sinus floor to provide a greater volume of bone to support dental implants.¹ Before implant placement, the bone volume should be radiographically evaluated. If an adequate amount of bone is not available for implant placement, bone grafting should be performed.¹

Laser therapy has been used for more than a century for

the treatment of skin conditions. However, recent studies have also demonstrated the efficacy of laser therapy for the treatment of articular, soft tissue, neural, skeletal, and vascular conditions. Recent studies have also confirmed the optimal efficacy of the light-emitting diode (LED) for the treatment of oral mucositis, dentin hypersensitivity, candidiasis, and disinfection of cavities following the removal of carious lesions.^{2,3}

Different types of bone materials are used as an alternative to autologous bone grafts for the reconstruction of the lost bone. **Hydroxyapatite** (HA) is one of the biomaterials used for this purpose, which is produced in different forms and compositions. Bone substitutes can be used in different forms. They can be applied in isolation, in combination with a membrane in guided bone regeneration, or with an autologous bone graft. Some techniques such as light therapy have been proposed to enhance bone healing.⁴ Evidence shows that irradiation of near infra-red wavelengths has a positive effect on bone healing compared with invisible light due to their greater penetration into tissues.⁴

LED and laser are structurally different. LEDs emit a narrow spectrum of electromagnetic radiation and possess non-coherent light. However, some studies have demonstrated similar photobiological effects of LEDs and lasers on wound healing when irradiated with similar exposure settings. Evidence shows that LEDs can serve as a suitable alternative to lasers due to advantages such as easy use and low cost.⁵ On the other hand, it has been shown that LED has the greatest effect on tissue osteoblasts in the process of wound healing.⁶ Another reason for suggesting LED as an alternative to a low-level laser (LLL) is that LED light is in the range of infrared and near-infrared wavelengths; thus, LED is a much safer choice than a laser.⁷

In general, new bone formation in the maxilla takes 6 to 9 months depending on the graft materials used in sinus lift surgery.⁸ An *in vitro* study indicated that laser therapy with a 650 nm wavelength had positive effects on the proliferation of stem cells.¹ Moreover, laser therapy with 780 nm and 810 nm wavelengths increased bone metabolism, protein synthesis, alkaline phosphatase activity, mineralization process, and activation of growth factors in the progenitor pulp cells.^{9,10}

Implant placement in a grafted area requires adequate bone in terms of quality and quantity.¹⁰ It would be ideal to find modalities to enhance bone regeneration to shorten the time required for osseointegration after implant placement.¹⁰ Low-level laser therapy (LLLT) and LED phototherapy have rarely been compared for bone regeneration. Thus, this randomized clinical trial aimed to assess the rate and maturity of the newly formed bone following LED phototherapy of a sinus lift area in humans. In general, the purposes of this article can be categorized as (1) Determination of osteogenesis under sinus lift and LED phototherapy, (2) Determination of bone formation

under sinus lift procedure without phototherapy with LED, and (3) Comparison of bone formation in sinus lift by allograft material with and without LED. If there is a significant difference in bone formation with the use of LEDs after the grafting process for a sinus lift, it can be argued that LED phototherapy before implant placement improves bone quality.

Materials and Methods

This randomized clinical trial (concurrent parallel) was conducted in accordance with the Declaration of Helsinki (1964). The study was approved by the faculty members at the Implant Department of Tehran University of Medical Sciences, and granted approval from the ethics committee of this university (IR.TUMS.REC.1394.1181). Volunteers were identified among the patients referred to the Implant Department of Tehran University of Medical Sciences to receive dental implant treatment. An appointment was set, and the purpose of the study was explained to the patients who were willing to participate in the study. Before the final reception, the dental and medical history of the patients was checked and each patient was examined by a prosthodontist and oral and maxillofacial surgeon to determine the qualification for participating in the study. Informed consent was obtained from all individual participants included in the study and additional informed consent was obtained from all individual participants whose identifying information is included in this article. The receptionist, prosthodontist, and oral and maxillofacial surgeon were blinded in the selection of the study group for the patients.

The pathologist, surgeons, and receptionist as well as the statistician were all blinded to the treatment process and patient groups.

The minimum sample size was calculated to be 22 for each intervention according to a study by Guzzardella et al,¹¹ using the mean comparison feature of Minitab software for sample size calculation assuming a standard deviation of 4.4 and minimum difference of 4.07. A total of 44 patients (18 females and 26 males between 30 and 50 years) presenting to the Implant Department of Tehran University of Medical Sciences, who required implant placement along with sinus lift surgery were selected and enrolled (Table 1 and Figure 1).

To avoid selection bias and to ensure that all individuals are randomly allocated to any group (experimental group (A) and control group (B)), a random sequence generator

Table 1. Demographic Characteristics of the Patients (After Allocation)

| | LED Group | Control Group |
|---------|------------|---------------|
| Age (y) | 40.5±8.5 | 41.5±6.5 |
| Gender | | |
| Male | 14 (63.6%) | 12 (54.55%) |
| Female | 8 (36.4) | 10 (45.5%) |

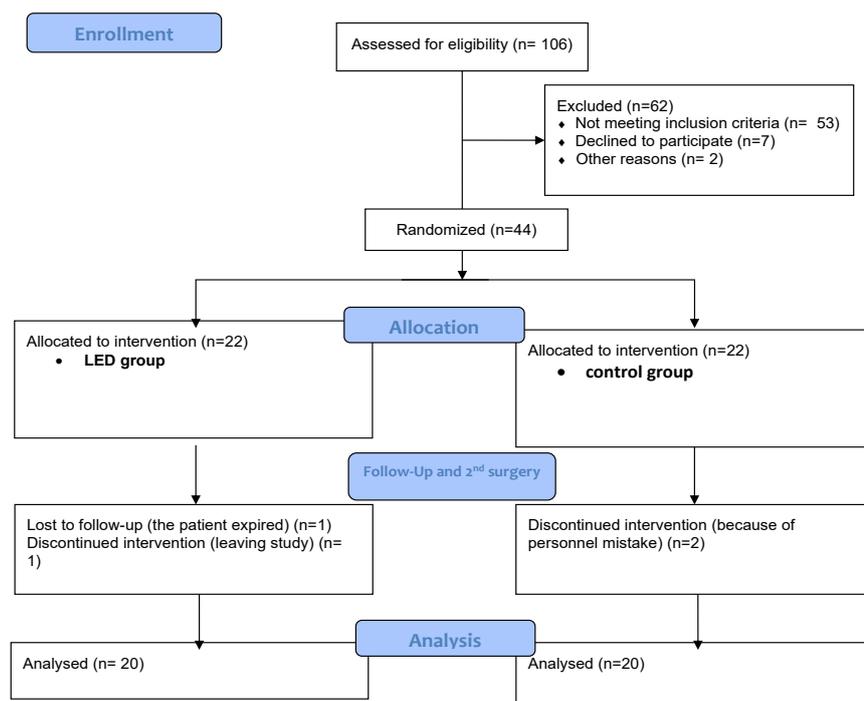


Figure 1. Flow Diagram of the Participants

program (<https://www.randomizer.org/tutorial/>) was used. Opaque envelopes were identified with each number and inside it a sheet containing the information of the corresponding experimental group was inserted according to the generated order. The numbers and codes were prepared and sealed in envelopes by a statistician of our institution before the trial. The generation of the sequence and the preparation of the envelopes were performed by a person who was not involved in the study. All surgeons were blinded to the meaning of the numbers.

The inclusion criteria were the absence of chronic sinusitis, absence of chronic bone marrow condition, no history of surgery at the site, absence of diabetes mellitus, no history of chemotherapy and radiotherapy, maxillary premolar edentulism, and signing informed consent forms.⁸ The exclusion criteria were smoking, chronic sinusitis, diabetes mellitus, history of cancer, use of bisphosphonates, and unwillingness to undergo LED phototherapy.⁸ Cone beam computed tomography showed the patients had D3 bone type, which is defined as the presence of a thin layer of cortical bone around a compact trabecular bone with adequate strength.

The patients were randomly divided into two groups (n=22) and underwent sinus lift surgery with the use of osteoconductive mineralized allograft (Kish Bone Material, Cenobone, 1000-2000 μm , Iran). After surgery, group A, according to the manufacturer's instruction, underwent LED phototherapy using a LED unit (Biolux Ltd, Vancouver, Canada) with a 620 nm wavelength in a continuous wave mode, red light, 25 mW/cm^2 power density, 30 J/cm^2 energy density, and 3.15 $\text{cm} \times 1.5 \text{ cm}$

= 4.73 cm^2 irradiated area (Figure 2). For this purpose, the device was adjusted and delivered to the patients. The patients were instructed on how to use it. The patients received LED phototherapy 20 minutes daily for a total of 21 days (total exposure time, 420 minutes). After termination of the 21 days, the device was adjusted for the



Figure 2. LED OsseoPulse and Patient Using the Device.

next patient and the disposable nose and earpieces were changed. Group B served as the control group and did not receive phototherapy. The patients showed up 6 months later for the second-stage surgery and implant placement. At this time, biopsy samples were obtained from the bone at the site of surgery during the surgical procedure of implant placement using a trephine bur with 2 mm diameter and 8 mm length. Implantium SLA implants (Dentium, Korea) were placed for the patients. The biopsy samples were placed in 10% buffered formalin for fixation. After 24 hours, they were decalcified using formaldehyde/formic acid solution (equal ratios of the two acids). Tissue specimens were sectioned into 4- μ -thick sections, stained with hematoxylin and eosin, and histologically evaluated for the amount of new bone formation and its maturity.

An oral and maxillofacial pathologist blinded to the study evaluated the specimens under a light microscope (Leitz DM - RBE Microscope, Leica Wetzlar Germany) at $\times 200$ magnification. The amount of inflammation was quantified and scored as follows: score 1: mild inflammation, score 2: moderate inflammation, and score 3: severe inflammation.

Histopathological assessment of the degree of inflammation was performed based on the observation of inflammatory cells in a specimen. Score 0 indicated the absence of inflammatory cells, score 1 indicated mild inflammation (number of inflammatory cells ≤ 25), score 2 indicated moderate inflammation (inflammatory cells between 25 to 125), and score 3 indicated severe inflammation (>125 inflammatory cells).¹²

The quality of bone was scored as follows: score 1: connective tissue containing blood vessels, fibroblasts, macrophages, and collagen fibers, 2: compact connective tissue and the presence of a high number of cells that differentiate into bone cells and indicate initiation of bone formation, 3: formation of new bone and compact connective tissue and 4: mature, newly formed bone.

The density of collagen fibers (maturity) was scored as follows: 1: absence of collagen fibers, 2: moderate density of collagen fibers, 3: high density of collagen fibers with no regular structure, and 4: high density of collagen fibers with a well-defined, organized structure.

Evaluation of the density of the collagen fibers was carried out by a pathologist who was blinded to the group allocation of patients under polarized light at $\times 100$ magnification. Scoring of collagen density was performed objectively based on pathological diagnosis; previous studies have not offered a classification system categorizing it as high, moderate and low density (Figures 3-6).

The data were analyzed using SPSS version 21 (SPSS Inc., IL, USA). Histopathological results were quantitatively analyzed using the Mann-Whitney U test.

Results

A total of 44 patients referring to at the Implant

Department of Tehran University of Medical Sciences were randomly assigned to the intervention and control groups. One patient expired during the study and one patient left due to personal reasons. One tissue specimen was lost due to an error in tissue processing, and one other tissue specimen was not adequate to prepare a slide (four specimens were lost). Eventually, 40 tissue specimens were analyzed; out of which, 20 belonged to the intervention and 20 belonged to the control group. Five patients underwent bilateral sinus lift surgery. Some degrees of inflammation were noted in both groups. A slight difference existed between the two groups in terms of the degree of inflammation, bone quality and maturity of collagen. According to the Mann-Whitney U test, the two groups were not significantly different in terms of the

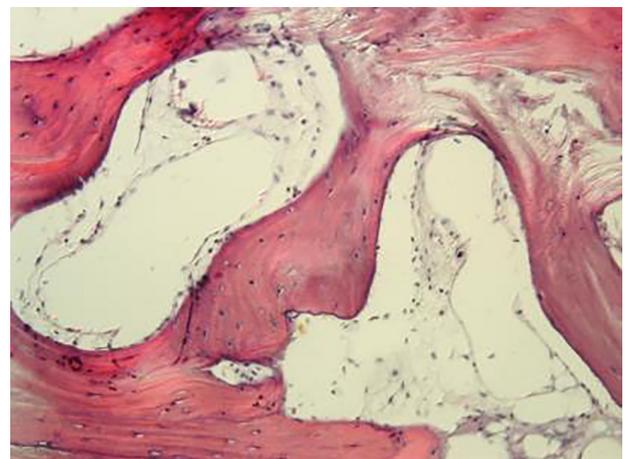


Figure 3. Mild Inflammation (Grade 1) With No Collagen Fiber (Grade 1) In-between the Host Bone (X200 Magnification).

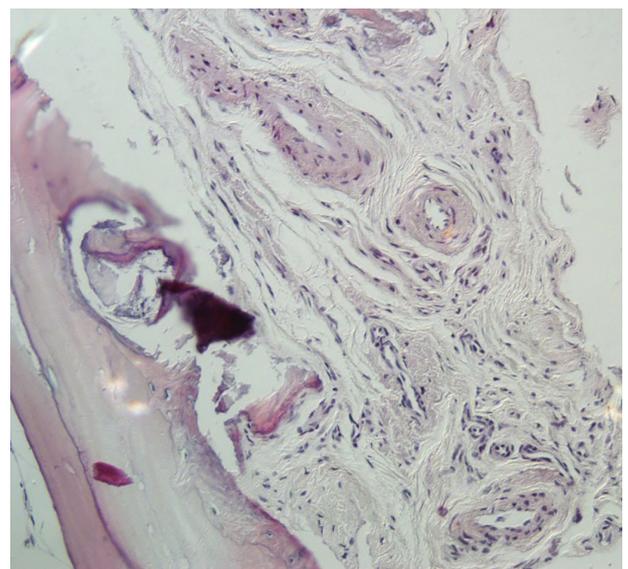


Figure 4. Mild Inflammation (Grade 1) With Moderately Matured Collagen Fibers (Grade 3) and Moderate Osteogenesis (Grade 3) ($\times 200$ Magnification)

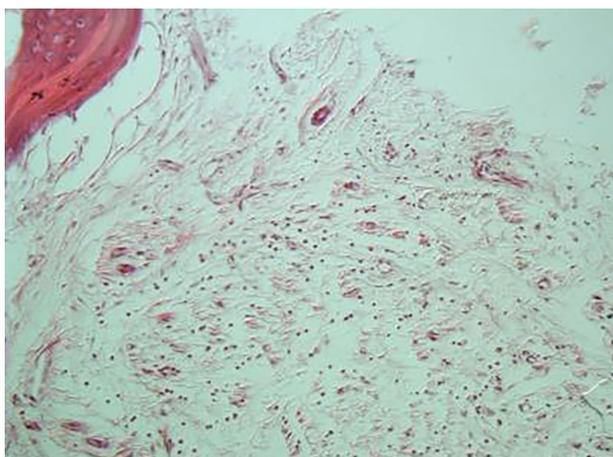


Figure 5. Mild Inflammation (Grade 1), Mature Fibers (Grade 4) and High Rate of Osteogenesis (Grade 4) (×200 Magnification).

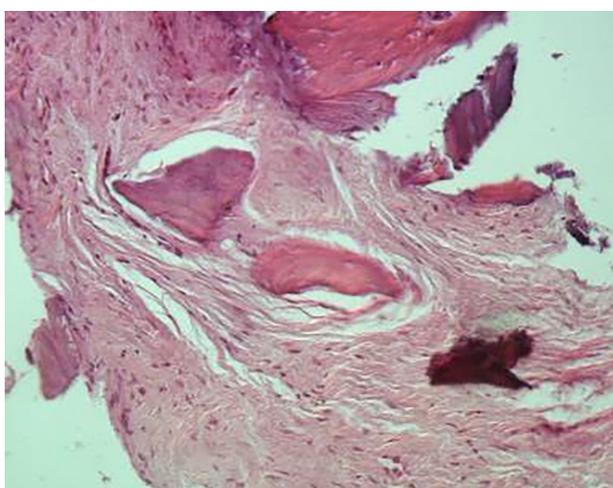


Figure 6. Moderate Inflammation (Grade 2) and Scarce Fibers (Grade 2) Adjacent to Host Bone (×200 Magnification).

degree of inflammation ($P=0.19$).

In the control group, no inflammation was noted in 75% of the patients while 25% showed some degrees of inflammation. In the LED phototherapy group, inflammation was not present in 55% while 45% showed some degrees of inflammation, and there were no significant differences between the two groups ($P>0.05$) (Table 2). The Mann-Whitney U test showed no significant difference in bone quality between the two groups ($P=0.65$, Table 3).

In the control group, 65% of the samples revealed high amounts of connective tissue along with a high number of giant cells, which indicated the initiation of differentiation into bone tissue. This value was 45% in the intervention group (Table 3).

The Mann-Whitney test showed no significant difference in the maturation of collagen fibers between the two groups ($P=0.96$). In terms of the maturity of collagen

fibers, collagen fibers were not seen in 45% of the slides in the control group while 65% of the slides in the test group showed a moderate density of collagen fibers (Table 4).

Discussion

Since the introduction of photo-biomodulation to medicine, several light sources have been evaluated for their efficacy to improve dental treatment outcomes in vitro and in vivo. The results of studies on this topic are mainly controversial, which may be due to the extensive range of irradiation parameters and the inability to quantify the potential effects of phototherapy with no bias.^{11,13-15} Considering the similarity between the effects of LLLT and LED phototherapy, we also evaluated studies that used LLLT; a small number of these studies had an in vitro design.^{16,17}

Table 2. Histological Results of Degree of Inflammation

| | | Laser * Inflammation Crosstabulation | | | |
|-------|-------|--------------------------------------|-------|-------|--------|
| | | Inflammation | | Total | |
| | | 1 | 2 | | |
| Laser | No | Count | 15 | 5 | 20 |
| | | % Within laser | 75.0% | 25.0% | 100.0% |
| | Yes | Count | 11 | 9 | 20 |
| | | % Within laser | 55.0% | 45.0% | 100.0% |
| Total | Count | 26 | 14 | 40 | |

Table 3. Histological Results of Degree of Osteogenesis (Bone Quality)

| | | LED * Bone Quality Crosstabulation | | | | | |
|-------|----------------|------------------------------------|-------|-------|-------|--------|--------|
| | | Bone Quality | | | | Total | |
| | | 1 | 2 | 3 | 4 | | |
| Laser | No | Count | 4 | 13 | 2 | 1 | 20 |
| | | % Within laser | 20.0% | 65.0% | 10.0% | 5.0% | 100.0% |
| | Yes | Count | 6 | 11 | 2 | 1 | 20 |
| | | % Within laser | 30.0% | 55.0% | 10.0% | 5.0% | 100.0% |
| Total | Count | 10 | 24 | 4 | 2 | 40 | |
| | % Within laser | 25.0% | 60.0% | 10.0% | 5.0% | 100.0% | |

Table 4. Histological Results of Degree of Bone Maturation (Collagen Maturation)

| | | LED* Collagen Maturation Crosstabulation | | | | |
|-------|----------------|--|-------|-------|--------|--------|
| | | Collagen Maturation | | | Total | |
| | | 1 | 2 | 3 | | |
| Laser | No | Count | 9 | 4 | 7 | 20 |
| | | % Within laser | 45.0% | 20.0% | 35.0% | 100.0% |
| | Yes | Count | 5 | 13 | 2 | 20 |
| | | % Within laser | 25.0% | 65.0% | 10.0% | 100.0% |
| Total | Count | 14 | 17 | 9 | 40 | |
| | % Within laser | 35.0% | 42.5% | 22.5% | 100.0% | |

In 2007, Brawn and Kwong-Hing histologically compared the extracted sockets grafted with hydroxyapatite and subjected to LED phototherapy compared with a control group without LED phototherapy. They used Biolux LED at a 605-631 nm wavelength and 20 mW/cm² power extra-orally for 21 days after the extraction. They placed a graft in the sockets. The study had a split-mouth design and one side served as the control and the other side served as the intervention group. After 35 days, the patients underwent the second-stage surgery for implant placement. During this procedure, a bone biopsy sample was obtained using a trephine bur, and bone regeneration at the site of phototherapy and the control side was histologically evaluated. Histological results showed increased new bone formation and faster disintegration of particles in the socket subjected to phototherapy. Faster bone healing at the socket grafted with hydroxyapatite and subjected to phototherapy enables faster implant placement at the site compared with a non-irradiated socket.¹⁸ A 6-month delay in our study can be one reason for no significant difference between the two groups. If implants had been placed sooner in our study, the earlier histopathological analysis might have revealed the positive efficacy of LED phototherapy for the enhancement of new bone formation in the sinus lift area.

Another study by Dereci et al compared the efficacy of phototherapy with blue light LED (with 400 to 490 nm wavelength, power density = 12 mW/cm², energy output = 13 J/cm² per session, 5 min each time for 6 days after the creation of calvarial defects) and Ga-Al-As low-level diode laser in terms of bone regeneration in rats with critical-sized calvarial defects. They used 30 Wistar albino rats and divided them into two groups of LED and LLLT. Next, they created critical-sized defects with 8 mm diameter in the calvaria of the rats and subjected them to phototherapy. After 21 days from the creation of defects, the rats were sacrificed and their calvaria was prepared for histopathological analysis. They used a computer program for histomorphometric assessment and measured the vertical and horizontal diameters of the newly formed bone at the site of defects. They also measured the diameter of the longest bone trabeculae formed at the site in millimeters. The results showed that both LED and LLLT groups experienced significantly higher osteogenesis in terms of the horizontal and vertical length of the newly formed bone compared with the control group ($P < 0.05$) while no significant difference was noted between LED and LLLT groups ($P > 0.05$). On the other hand, a significant difference was noted in the length of bone trabeculae between the LLLT and control groups while no significant difference was noted between LED and control or between LLLT and LED groups ($P < 0.05$). In general, the results showed that LED blue light enhanced osteogenesis at the defect sites, but bone regeneration was not significantly different between LED and LLLT groups.¹⁹ Their results were different from

ours, which may be due to the use of different exposure parameters and duration of each session. However, their results confirmed that LLLT and LED had therapeutic and biological effects on human cells.

Jakse et al performed sinus lift surgery and then used intraoral LLLT. They indicated that the application of LLLT caused no significant effect compared with the control group. The type of laser used by Jakse et al was LLL (3-4 J/cm²). Considering the low output power of the laser, one possible explanation for the inefficacy of the laser in this study may be the cortical sinus walls that absorb the majority of radiation and decrease the energy density of radiation received by the tissue.²⁰ This justification was confirmed by the histomorphometric findings because LLLT had a positive effect on the percentage of stained osteocytes subjected to radiation while no significant effect was noted on the posterior sinus wall that received much lower radiation.²⁰ Another explanation for the equal rate of osteogenesis in the two groups may be the 6-month time lapse. There is a possibility that osteogenesis occurred faster on the case side at first. However, we had no choice other than taking the biopsy samples during the second-stage surgery for ethical considerations.

In 2012, Peng et al evaluated the effect of red LED light on bone marrow mesenchymal stem cells in the presence and absence of osteogenic supplements. The samples were divided into four groups and each group was irradiated with LED light with 0, 1, 2, and 4 J/cm² energy density. Cell proliferation was evaluated using fluorescence staining. They stated that non-coherent red light can stimulate cell proliferation but cannot induce differentiation of mesenchymal stem cells to osteoblasts in a normal medium in the absence of osteogenic factors. However, it enhanced the differentiation of mesenchymal stem cells to osteoblasts and decreased the proliferation of mesenchymal stem cells in the media containing osteogenic supplements.²¹

The selection of a LED device with a 620 nm wavelength in our study was based on previous studies that demonstrated that red LEDs have several effects on cells and activate the fibroblast growth factor, increase type I procollagen and increase the number of fibroblasts. Also, the red LED has the deepest penetration into the tissues among the visible LED spectra. Thus, it was suitable for use in our study since we indirectly irradiated the LED extra-orally and laterally to the maxillary sinus area. Mild infiltration of inflammatory cells was histologically noted after the red LED radiation and may explain the presence of mild inflammation in bone samples.⁵ Inefficacy of LED in our study may be due to the following reasons: Based on the available literature about phototherapy, three parameters are important to achieve a favorable result in LED phototherapy: (I) selection of a proper wavelength of light for the target cells or chromophores because if the wavelength is not correctly selected, favorable absorption does not occur, and the subsequent reactions in target

cells do not take place; (II) the intensity, density and power (W/cm^2) of photons should be properly adjusted to enable their adequate absorption by the cells, and (III) adequate dosage or fluence (J/cm^2) should be adjusted to obtain ideal energy density. Another important parameter is the penetration depth of LED light and its duration of use. LED light radiated to the target site intraorally may yield different results.²²

Our study had some limitations such as a small sample size since some patients did not consent to the second-stage surgery due to financial issues, time shortage, hygienic problems, and so on. Moreover, we could not make sure that all patients regularly used the device daily and in a correct manner. Furthermore, it was difficult to persuade patients to take part in the study. Another possible reason that may explain the inefficacy of LED phototherapy in our study was the position of the zygomatic bone in some patients, which prevented correct positioning of the device as well as the high thickness of zygomatic bone and sinus walls, which might have limited the penetration depth of radiation and decreased its energy.

Future studies with a larger sample size are required to perform the bone biopsy in a shorter time after sinus lifting to minimize the effect of confounders.

Conclusion

The results of this study which investigated the effect of LED on ossification after sinus lift surgery revealed no statistically significant differences in ossification and bone maturation between the two groups with and without LED phototherapy.

Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by GS, MA, ZG, KR and PAS. The first draft of the manuscript was written by MA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical considerations

The reason and number of follow-up visits were explained to the patients, and the follow-ups were scheduled with their consent. Laser therapy was performed for patients at no cost. The research protocol was approved by the ethics committee of Tehran University of Medical Sciences. Patients freely signed informed consent forms to participate in this study. The study was also registered in the *Iranian Registry of Clinical Trials website* (identifier: IRCT20180222038827N1; <https://www.irct.ir/trial/29772>)

Conflict of Interests

The authors declare that they have no conflict of interest.

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References

1. AlGhamdi KM, Kumar A, Moussa NA. Low-level laser therapy: a useful technique for enhancing the proliferation of various cultured cells. *Lasers Med Sci.* 2012; 27(1):237-49. doi: 10.1007/s10103-011-0885-2. Epub 2011 Jan 28.
2. Barolet D. Light-emitting diodes (LEDs) in dermatology. *Semin Cutan Med Surg.* 2008; 27(4):227-38. doi: 10.1016/j.sder.2008.08.003.
3. Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy - an update. *Dose Response.* 2011;9(4):602-18. doi: 10.2203/dose-response.11-009.Hamblin.
4. Soares LG, Aciole J, Aciole G, Barbosa A, Silveira-Júnior L, Pinheiro A. Raman study of the effect of LED light on grafted bone defects. *SPIE.* 2013;8569. doi:10.1117/12.2002584.
5. Opel DR, Hagstrom E, Pace AK, Sisto K, Hirano-Ali SA, Desai S, et al. Light-emitting Diodes: A Brief Review and Clinical Experience. *J Clin Aesthet Dermatol.* 2015;8(6):36-44.
6. Pagin MT, de Oliveira FA, Oliveira RC, Sant'Ana AC, de Rezende ML, Greggi SL, et al. Laser and light-emitting diode effects on pre-osteoblast growth and differentiation. *Lasers Med Sci.* 2014;29(1):55-9. doi: 10.1007/s10103-012-1238-5.
7. Rosa CB, Habib FA, de Araújo TM, Dos Santos JN, Cangussu MC, Barbosa AF, et al. Laser and LED phototherapy on midpalatal suture after rapid maxilla expansion: Raman and histological analysis. *Lasers Med Sci.* 2017;32(2):263-274. doi: 10.1007/s10103-016-2108-3.
8. Rahpeyma A, Khajehahmadi S. Comparative evaluation of implant fixture length in open sinus lift procedure simultaneously with delayed placement. *J Dent Implant.* 2013;3:122-4. doi: 10.4103/0974-6781.118894.
9. Gao X, Xing D. Molecular mechanisms of cell proliferation induced by low power laser irradiation. *J Biomed Sci.* 2009;16(4):1-16. doi: 10.1186/1423-0127-16-4.
10. Karu TI. Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. *IUBMB Life.* 2010;62(8):607-10. doi: 10.1002/iub.359.
11. Guzzardella GA, Fini M, Torricelli P, Giavaresi G, Giardino R. Laser stimulation on bone defect healing: an in vitro study. *Lasers Med Sci.* 2002;17(3):216-20. doi: 10.1007/s101030200031.
12. Pretel H, Lizarelli RF, Ramalho LT. Effect of low-level laser therapy on bone repair: Histological study in rats. *Lasers Surg Med.* 2007;39(10):788-96. doi: 10.1002/lsm.20585.
13. Mikhail FF, El-Din M, Ibrahim T, Zekry K, Nemat A, Nasry S. Effect of Laser Therapy on the Osseointegration of Immediately Loaded Dental Implants in Patients under Vitamin C, Omega-3 and Calcium Therapy. *Open Access Maced J Med Sci.* 2018;6(8):1468-74. doi: 10.3889/oamjms.2018.291.
14. Lagan KM, Clements BA, McDonough S, Baxter GD. Low intensity laser therapy (830nm) in the management of minor postsurgical wounds: a controlled clinical study. *Lasers Surg Med.* 2001;28(1):27-32. doi: 10.1002/1096-9101(2001)28:1<27::AID-

- LSM1013>3.0.CO;2-4.
15. Karu TI. *The Science of Low-Power Laser Therapy*. Gordon & Breach Science Publishers; 1998.
 16. Basford JR. Low intensity laser therapy: still not an established clinical tool. *Lasers Surg Med*. 1995;16(4):331-42. doi: 10.1002/lsm.1900160404.
 17. Sella VR, do Bomfim FR, Machado PC, da Silva Morsoleto MJ, Chohfi M, Plapler H. Effect of low-level laser therapy on bone repair: a randomized controlled experimental study. *Lasers Med Sci*. 2015;30(3):1061-8. doi: 10.1007/s10103-015-1710-0.
 18. Brawn PR, Kwong-Hing A. Histologic comparison of light emitting diode phototherapy-treated hydroxyapatite-grafted extraction sockets: a same-mouth case study. *Implant Dent*. 2007;16(2):204-11. doi: 10.1097/ID.0b013e318065a84c.
 19. Dereci Ö, Sindel A, Serap Toru H, Yüce E, Ay S, Tozoğlu S. The Comparison of the Efficacy of Blue Light-Emitting Diode Light and 980-nm Low-Level Laser Light on Bone Regeneration. *J Craniofac Surg*. 2016;27(8):2185-2189. doi: 10.1097/SCS.00000000000003068.
 20. Jakse N, Payer M, Tangl S, Berghold A, Kirmeier R, Lorenzoni M. Influence of low-level laser treatment on bone regeneration and osseointegration of dental implants following sinus augmentation. An experimental study on sheep. *Clin Oral Implants Res*. 2007;18(4):517-524. doi:10.1111/j.1600-0501.2007.01369.x.
 21. Peng F, Wu H, Zheng Y, Xu X, Yu J. The effect of noncoherent red light irradiation on proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells. *Lasers Med Sci*. 2012;27(3):645-53. doi: 10.1007/s10103-011-1005-z.
 22. Kim WS, Calderhead RG. Is light-emitting diode phototherapy (LED-LLLT) really effective. *Laser Ther*. 2011;20(3):205-15. doi: 10.5978/islsm.20.205