Title: LLLT Effects on Inferior Alveolar Nerve (IAN) Recovery Post-orthognathic Surgery

NCT04910074
IRB#: 2021-12990
IRB Approval Date: 03/16/2022

Background and Significance

Orthognathic surgery is an essential part of correcting dentofacial deformities. The most common surgery for correcting mandibular deformities is the bilateral sagittal split osteotomy (BSSO). The BSSO was first developed in 1957 by Obwegeser(1), and allowed for anteroposterior correction of the mandible in either a Class II or Class III direction. The BSSO has been modified over time to improve surgical stability and reduce negative post-operative sequelae. Despite the modifications, there are still several potential complications that patients may experience. The most common post-operative complications are pain, swelling and nerve dysfunction.

As with any surgery, pain and swelling are unavoidable, but the extent can be variable. A variety of both pharmaceutical and non-pharmaceutical approaches are generally used to improve pain and swelling, including warm compresses, pressure dressings and analgesics. Physical interventions may reduce swelling, which in turn reduces pain, but are limited in their penetration. Meanwhile medications carry their own potential negative consequences; opioids carry a risk for dependence and neutropina and non-steroidal anti-inflammatories can cause digestive issues, renal problems.

Nerve dysfunction leading to neurosensory deficits are a relatively common side effect of a BSSO, with literature estimating rates between 9% to 84.6% (2, 3) The inferior alveolar nerve (IAN) runs through the mandibular canal in the body of the mandible, with a branch, the mental nerve, splitting off and exiting the bone at the mental foramen between the first and second premolars. The IAN provides sensation to the gingiva and teeth, while the mental nerve provides sensation to the lips and the chin. During the BSSO, the IAN is necessarily moved and is at risk for either direct or indirect injury, which leads to the neurosensory deficits which are usually transient, but can be permanent in some cases (4-7). Therapy for IAN dysfunction is limited.

One treatment modality that has solid evidence to treat both sensory nerve dysfunction and pain is low-level laser therapy (LLLT). LLLT has been established as viable therapy that modulates the body's own healing potential in recovery from injury and surgery. The proposed mechanism of LLLT is that low intensity laser light applied to body tissues penetrates and scatters into the tissue, and the scattered energy stimulates a cascade reaction that leads to upregulating of healing and a reduction of inflammation (8).

Existing studies have shown that LLLT can modulate the post-surgical healing and pain (9, 10) and nerve recovery in orthognathic surgery patients (11-15,). Two systematic reviews have also determined that LLLT is an efficacious therapy to reduce pain and have significant long-term improvement neurosensory deficits over placebo (16, 17). Additionally, the literature has a consensus that the adverse effects of LLLT are virtually non-existent, with both review papers noting no negative complications reported in any of the papers included in the reviews. Both review papers, however, discuss that the existing literature has too few studies that are well-designed. Both review articles recommended more objective analysis of neurosensory function, as many relied on objective patient reports, and a longer follow-up period. Additionally, many studies have been conducted using a split-mouth design, in which one side receives LLLT and the other side doesn't, in order to increase the sample size without increasing the number of patients. The issue is, according to the current understanding of LLLT (8, 9), the photobiomodulation effect can travel away from the site of LLLT administration. There are no documented adverse effects of LLLT.

This study would aim to study the effects of LLLT on pain, swelling and neurosensory function on patients who have undergone orthognathic surgery with BSSO and compare the effects on a control group of patients undergoing similar surgery who will not receive any extraordinary post-op care.

Hypothesis

Administration of low-level laser therapy along the skin over the mandibular body of patients who have had bilateral sagittal split osteotomy surgery for correction of the position of the mandible will reduce pain and swelling and improve neurosensory dysfunction when compared to patients who do not receive the laser treatment.

Study Design

The study will have two groups into which patients will be assigned to a control group and an experimental group through a random number generator. Patients will undergo their planned surgical procedure and receive instructions as per standard clinic protocols, in both pre- and post-operative settings. The standard instructions include information on pain and swelling management. The patients will also receive post-operative medications, including an NSAID and an opioid for pain management and a steroid to reduce inflammation and swelling. The patients will be seen at one-week intervals for six weeks for post-operative follow-ups, as per standard clinic protocols. The experimental group will undergo low level laser therapy (LLLT) at weekly intervals. Subject treatment assignments will remain blinded until the final subject has completed follow up and all data has been recorded and validated. Urgent, immediate unblinding due to medical emergency may be authorized by the Investigator. When possible, the treatment assignment will be provided to the treating physician in order to maintain the blind for the Investigator and study staff. All instances of subject unblinding will be documented in the study record.

The proposed LLLT protocol will use the Biolase Epic X, an InGaAsP diode laser (940nm) using the pain relief handpiece, a device which has received FDA approval (GUDID 00647529002537) for the treatment of pain, muscle relaxation and healing via increased local circulation. The LLLT will be administered to the experimental group at 30 j/cm2. The laser will be applied extraorally, on the skin overlying the mandible. Application will be for 40 seconds per side, with 10 seconds administered in four places along the jawline, 1 cm apart starting from the gonial angle. The timing would coincide with standard post-operative care, with the first LLLT administration performed on post-operative day 1, prior to the patient's discharge from the hospital. The follow-up LLLT doses would be given at the standard post-op follow-up visits, at one-week intervals, which would be at week 1, week 2, week 3, week 4, week 5, and week 6. Patients will be seen for evaluation at week 8 and again at approximately 20 weeks post-surgery. The control group will follow the same post-op visit schedule, but receive a dummy treatment in which the laser handpiece is moved over the patient's jaw in a similar fashion as the experimental but without laser irradiation.

Nerve function, pain and swelling will be measured according to objective measures. A baseline measurement will be recorded pre-operatively for nerve function and pain. Baseline for swelling will be used from the final measurement at week 8, due to the changes in mandible length caused by the orthognathic surgery. Measurements for each outcome will also be performed on the days for which

LLLT is administered. The individual who performs the assessment will be blinded to the group to which each patient belongs.

To evaluate nerve function, three tests will be conducted, a two-point discrimination (TPD) test, a hard stimulus test and soft stimulus test. For the TPD test, the patient will be instructed to close their eyes, and a caliper will be placed on the lateral aspect of the patient's chin. The calipers will start at 0 mm and be incrementally opened in .5mm increments, and the first distance felt by the patient as two distinct points will be recorded reported in millimeters. For the soft- and hard- stimuli tests, the lower face will be divided into eight regions, with four symmetric regions per side. Region 1 will be from the skin on the chin at the midsagittal plane laterally 1 cm. Region 2 will be the skin from the edge of Region 1 extending laterally 1 cm. Region 3 will be the skin from the edge of Region 2 extending laterally 1 cm. Region 4 will be the vermillion of thee lower from the midsagittal plane to the commissure. The regions will be designated by an "L" for left or "R" for right, plus a number as per the above scheme. Each region will be checked for nerve function via two tests, a cotton-swab test and a two test. During the evaluation, the patient will be instructed to keep their eyes closed. The cotton-swab test will involve the skin in each region being lightly brushed in a 2cm vertical path twice per region, and the patient reporting if they feel the contact. Likewise, the toothpick test will involve the skin being slightly depressed by the edge of a toothpick in three spots separated by 1 cm each per region, and the patient reporting if they feel the contact. The responses will be recorded as positive or negative for soft (swab) or hard pressure (toothpick), by region.

Pain will be reported via use of a visual analogue scale (VAS). The patient will rate the intensity of the pain on each side of the mandible at each visit. The intensity of the pain will be from zero, meaning compete absence of pain, to 10, indicating the maximum amount of pain imaginable.

Swelling will be measured with a soft measuring tape from the tip of the chin to the lower lobe of the ear, bilaterally. The calculation of the swelling index will be done by subtracting the baseline length (from the six-week post-operative visit) to the measured length and diving the difference by baseline length and multiplying by 100.

Outcomes (primary and secondary)

In this study, the predictor variable was the use of laser therapy versus placebo treatment after orthognathic surgery on the mandible. The primary outcome variable was neurosensory disturbance recovery by the TPD, hard and soft sensory tests. The secondary outcome variables are pain reduction, as measured by change in VAS, and swelling reduction, as measured by soft-ruler measurement of lower face.

Sample Size

Published data (13-15) examining the effect of LLLT on IAN functional recovery shows a range of improvement versus placebo. The percentage of recovery shows that the LLLT treatment led to 27.3% (n=30, not split mouth, standard deviation not reported) (13), 13% (n=12, split mouth, 7.4167 ± 1.62 vs 8.5000 ± 1.56) (14), and 15% (n= 15, 5.12 $\pm$ 0.59 vs 5.97 $\pm$ 0.45) (15) improvement in sensory function, with . Additionally, one non-placebo controlled study of patients with long-standing documented neurosensory alteration following dental surgery (12) showed 33% improvement over baseline (n=4).

Using these studies, a sample size graph (Figure 1) was plotted in R Stats Package with the effect size versus sample size, with the standard deviation set to 0.5 and power set to 0.9. In order to detect an effect size of 0.5 with a SD of 0.5 at 90% power a sample size of just over 22 is needed. Therefore, 23 subjects per arm is required.

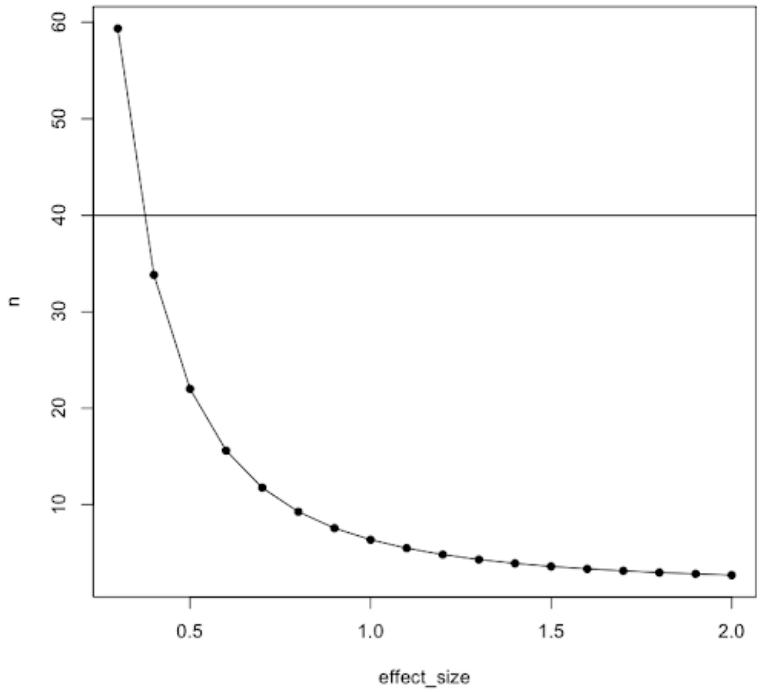

Figure 1- Effect size vs. Sample size.

The oral surgery clinic at Jacobi Medical Center treats approximately 50 patients with orthognathic surgery of the mandible annually, and has done so routinely for the last decade. Recruiting 46 patients to participate, even accounting for potential drop outs or failure to follow-up, should prove feasible.

Risk/Benefit

There are no known risks to low-level laser therapy.

The potential benefits to the patients are improved course of healing after orthognathic surgery.

Data will be stored on Jacobi shared servers using password-protected spreadsheets, that use codes to de-identify patients' names. The list of patient names that correspond to codes will be saved separately in a password-protected spreadsheet, and only the PI will have access the password.

Participant Recruitment

The patient pool for this study will be drawn from regular patients scheduled to undergo orthognathic surgery at Jacobi Medical Center. Patients who have been cleared for orthognathic surgery already must be in good health and understand the risks of the surgery. The only additional requirements for inclusion are 1) the planned surgery includes bilateral sagittal split osteotomies; 2) patients must be free from pre-operative inferior alveolar neurosensory deficiencies; 3) the patient cannot have an intra-operative

accidental fracture or rupture of the inferior alveolar nerve. The details of the whole orthognathic surgery will be recorded (including maxillary procedure, genioplasty, and direction of positional change of the mandible) but will not alter eligibility for enrolment in the study.

Since 2013, over 30% of the patients treated for orthognathic surgery at Jacobi Medical Center are between the ages of 15 and 18, which is in line with orthognathic surgery in general. As such, the study aims to include these patients in the potential pool of subjects. Because of the significant portion of patients under the age of 18 in general, and their inclusion will allow for age to be examined as a related factor in how healing proceeds. Their inclusion will also allow for an adequate sample size.

Informed Consent

Patients who express interest in volunteering for the study will have the risks and benefits of the study explained to them, as well as that they may be assigned to either a control or experimental group. The details of study participation will be explained, including that the patients will not have any aspect of their surgery or post-care altered, other than LLLT treatment. It will be explained that the time commitment of the study is the same as the normal post-op care, with the exception of two additional visits at 8 weeks and 20 weeks post-op. It will be explained that patients may decided to not volunteer and their treatment will not be affected. Likewise, if the patients decide to drop out of the study, their treatment will not be affected. Information security will also be discussed with the patient during the consent process. All information in the discussion will be provided to the patient in written form, with a copy for them to keep. Patients who desire an alternate language will be offered translation services.

Patients over 18, will be given an informed consent form to sign. Patients who are under 18 will be asked to sign the informed consent form, to indicate their assent, while a legal guardian, who will also be present for the discussion of the risks and benefits of the study, will be asked to sign for consent.

Data analysis

The primary outcome, change in neurosensory deficit, is measured by the three clinical tests, TPD, soft-stimulus and hard-stimulus. For TPD, the difference between the LLLT group and placebo group at each time point will be compared using an independent t-test, with alpha set at .05. The soft- and hard-stimulus tests for each region will be analyzed at each time point with a chi-square test. VAS pain score and swelling index will be analyzed using independent t-tests for the measurements on each side at each time point, with alpha set at .05. Linear regression will be performed to analyze the relationship of the pain, swelling and nerve tests with age, skeletal class, direction and magnitude of mandibular movement, and inclusion of genioplasty.

Safety monitoring

While low-level laser therapy has no known adverse effects, safety monitoring of the study participants will be conducted in conjunction with their normal post-operative care during the duration of their participation, which occurs at each post-surgical visit. As orthognathic post-op care is generally overseen by the Jacobi Director of Oral & Maxillofacial Surgery (OMFS), the director will serve as the safety monitor. Adverse events during post-op care are reported to the Director of OMFS and documented into the patient chart. Any patient reporting an adverse event that is deemed, by the Director of OMFS, as clinically significant, will be withdrawn from the study and provided with all appropriate treatment. If more than one patient is withdrawn from the study through this mechanism, the study will be halted.

The Director of OMFS will report to the PI any adverse events requiring removal of a patient from the study, and the PI will document the adverse effects and provide a report to the IRB.

Citations

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