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ORIGINAL ARTICLE

A Randomized Triple-Blind Clinical Trial of the Effect of Low-Level Laser Therapy on Infiltration Injection Pain in the Anterior Maxilla

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ABSTRACT

Objective: To evaluate the level of pain experienced during infiltration anesthesia of the anterior maxilla following low-level laser therapy (LLLT) with 810-980 nm wavelengths. **Material and Methods:** In the current triple-blind clinical trial, 84 patients received a total of 168 infiltration anesthesia injections (1.8 mL of 2% lidocaine plus 1:100,000 epinephrine) in the anterior maxilla. Each patient received two injections into the buccal mucosa of the right and left central incisors with a two-week interval. One injection was performed after LLLT, while the other injection was administered conventionally without laser. The pain level was measured immediately after injection using a visual analog scale (VAS). **Results:** There was a significant difference in the pain level experienced with and without LLLT, such that the mean pain score following LLLT was significantly lower than that without LLLT ($p<0.05$). No significant difference was found in the pain level between laser and no laser groups in males, but the difference in this regard was significant in females ($p<0.05$) and female patients experienced a significantly lower level of pain following LLLT. **Conclusion:** The low-level laser therapy can be successfully used to decrease the level of pain experienced during infiltration anesthesia of the anterior maxilla.

Keywords: Pain; Injections; Anesthesia, Local; Low-Level Light Therapy; Maxilla.

Introduction

Providing adequate depth of local anesthesia is an important skill for dental clinicians. The anesthetic injection is probably the most important cause of dental fear in patients. Minimizing the level of pain and discomfort experienced by patients during anesthetic injection remains a challenge for almost all dental clinicians. Reaching sufficient depth of local anesthesia with minimal pain and discomfort requires adequate knowledge about the anatomy of the nervous system in the area, anesthetic agents and the available techniques [1-3]. Anesthetic injection pain has a negative impact on patient cooperation, while successful anesthesia can increase patient cooperation and facilitate the provision of dental treatments [4]. Dental clinicians should have adequate knowledge about pain control methods to minimize the level of pain experienced by patients during the anesthetic injection. Factors such as needle gauge, the temperature of the anesthetic agent, the pH at the site of anesthetic injection, and the type of anesthetic agent can all affect the level of pain experienced by patients in this procedure [5-8].

Considering the significance of pain control during anesthetic injection, many studies have suggested strategies to decrease pain during infiltration anesthesia, such as mild vibration of the needle, massaging the mucosa at the injection site, controlled injection by use of a vibration device, application of topical anesthetic agents to decrease pain during injection and comparison of different injection techniques at the same site to find the technique with the lowest level of pain [9,10].

The application of LLLT to decrease pain and tissue healing dates back to 30 years ago [11,12]. However, LLLT is a novel technique in dentistry that is gaining increasing popularity [13,14]. LLLT is non-invasive and painless. It has insignificant side effects similar to a placebo and no serious reported consequences [15]. LLLT has several clinical applications, such as prevention of pain, swelling and trismus following third molar extraction and periodontal surgery, pain relief following adjustment of orthodontic appliances, curing chronic facial pain, chronic sinusitis, gingival inflammation, herpes simplex, tooth hypersensitivity and sensory disturbances of the inferior alveolar nerve [13,16,17]. The results of studies on the efficacy of LLLT are controversial [18]. Some studies have confirmed its positive efficacy, while others reported its clinical inefficacy [19,20]. However, the efficacy of LLLT depends on factors such as wavelength, tissue type, duration of use and dosage of laser [14].

A study on the dosage of LLLT has shown that different wavelengths of laser have different penetration depths into the skin [21]. One mechanism of action of LLLT for pain reduction is changing the action potential of peripheral nerves. It decreases the velocity of conduction of fast axons and lowers the potential of mitochondrial membrane, resulting in decreased access to ATP and neural insufficiency of A-delta and nociceptive nerve fibers [22]. Another mechanism of action of LLLT in pain reduction is stimulation of the production of beta-endorphins [23]. Beta-endorphin is a natural mediator produced by the human body to decrease pain. It also inhibits the release of arachidonic acid, which affects the injured cells to produce metabolites interacting with pain receptors [24].

No consensus has been reached on ideal parameters for LLLT [22]. Also, information regarding pain reduction by LLLT, especially the pain level experienced during anesthetic injection, is limited [25]. Thus, in this study, we assessed the effectiveness of LLLT for pain reduction during anesthetic injection in the anterior maxilla.

Material and Methods

Trial Design, Participants, Sample Size

This triple-blind, crossover trial evaluated 84 patients (41 females and 43 males) who required bilateral restoration of their maxillary central incisors presenting to the Restorative Dentistry Departments of School of Dentistry, Kermanshah University of Medical Sciences. The results of previous studies were used to calculate the sample size. In the study of Ghaderi et al. [25], the standard deviation of VAS scores in the experimental and control groups was 2.9 and 2.7, respectively. Considering $\alpha = 0.05$ and power 90% - $\beta = 1\%$, the minimum sample size was 84 (42 in each group). The sample size was calculated by PASS sample size software version 15 (NCSS LLC, Kaysville, Utah, USA) according to the following formula:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(S_1^2 + S_2^2\right)}{(\bar{X}_1 - \bar{X}_2)^2}$$

Inclusion and Exclusion Criteria

The inclusion criteria were general health, no allergy to lidocaine, and no intake of sedatives or antidepressants within the past two weeks. Participation in the study was voluntary, and patients were free to quit at any time. All patients signed informed consent forms prior to enrollment.

Interventions

Infiltration anesthesia was administered adjacent to the apex of maxillary central incisors twice with a 2-week interval. The first operator determined the laser settings (LLL; Quicklase Ltd., Canterbury, UK) based on the patient's group allocation in the first session. The laser settings were as follows: 12 W dual continuous-wave, 810+980 nm, 4 J/cm² energy, 50 mW, 810 nm, 100 mW, 810-980 nm or +50 mW, 980 nm, or 0 mW for the control site, 90 s time, 225 mm² cross-sectional area and contact mode with no pressure with laser hand-piece positioned perpendicular to the site.

The second operator, who was blinded to the group allocation of patients and laser settings, applied laser and, immediately after laser irradiation, administered 2% lidocaine with 1:100,000 epinephrine (Darupakhsh Pharmaceutical Co., Tehran, Iran). All cartridges were stored at room temperatures (21 °C). The anesthetic agent was injected at the depth of the vestibule and around the root of maxillary central incisors under equal conditions (the bevel of needle was towards the bone, a 27-gauge short needle was used, needle was penetrated into the tissue for 2-4 mm and the injection took 1 minute). In both the intervention and control sides, laser application was associated with light and noise. However, the laser power was 0 mW in the control side. All injections were performed under similar conditions by the same operator.

Outcome Assessment

The level of pain experienced by patients was evaluated immediately after the injection using a 0-170 visual analog scale (VAS). Before injection, the subjects were asked to score their pain through a Heft-Parker visual analogue pain scale (VAS). The VAS scores were classified into four classes (Figure 1). No pain: 0 mm, mild pain: > 0 mm and ≤ 54 mm, moderate pain: > 54 mm and < 114 mm, and severe pain: 114 mm or more. A third operator assessed the pain scores of patients.

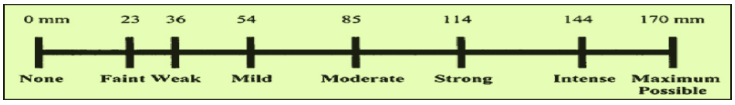

Figure 1. Heft-Parker VAS was used for the assessment of pain scores. The millimeter numbers are not shown on the VAS forms used by the patients.

Allocation, Randomization, Blinding

This study was carried out as a crossover design; each person was his/her own control. The participant received injection with or without laser irradiation by random assignment. Selection of the right/left side for the first injection and use or no use of laser for the first injection were determined randomly by the sealed envelope technique. Two sets of envelopes (n=84) were used for this purpose. The first set included 42 "A" and 42 "B" cards. "A" indicated the right quadrant and "B" indicated the left quadrant. The second set included 42 "C" and 42 "D" cards. "C" indicated the intervention (laser) side and "D" indicated the control side. Each patient drew two envelopes, one from each set, which determined the side of the first injection and use/no use of laser in the first session. The reverse was performed in the second session. The study had a triple-blind design since the patient, the operator who performed the injection and the statistician were blinded to the group allocation of sites.

Statistical Analysis

Kolmogorov-Smirnov test checked the normal distribution of data using SPSS version 18 (SPSS Inc., IL, USA) via independent t-test and paired t-test Significance level was set at 0.05.

Ethical Clearance

The research was approved by the ethics committee of Kermanshah University of Medical Sciences (IR.KUMS.REC.1397.348) and registered at the Iranian Registry of Clinical Trials (IRCT33332).

Results

Eighty-four patients, including 43 males (51.2%) and 41 females (48.8%) participated in this study. The mean age of participants was 24.76±2.63 years. Based on the Kolmogorov-Smirnov test, normal distribution of data was confirmed (p>0.05). The average age was 24.53±1.97 years in females and 24.98±3.14 years in males. The difference in the average age of males and females was not significant (p=0.437).

Table 1 shows the period effect and the carry-over effect on patients' pain score. First, the period effect on pain score was evaluated. An independent t-test was applied to analyze the difference in the mean pain scores between the two orders of injection. According to the findings, the period effect was not significant (p=0.840). In other words, the patients' condition and response remained the same in the second injection compared with the first injection. Next, the carry-over effect was evaluated. Independent sample t-test compared the mean pain scores of patients between the two orders of injections, which showed no significant carry-over effect (p=0.332). Thus, the interaction effect of type of injection and period on pain score was not significant. Furthermore, the amount of pain was not significant under one order of injection in the first and second periods. The laser therapy reduces moderate pain and has no effect on mild pain (Figure 2).

Table 1. Period effect and the carry-over effect on the pain score of patients.

Order of the Injection	Pain with Laser		Pain without Laser		Pain Difference (With Laser without Laser)		Mean of Pain (With Laser + without Laser)/2)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BA	33.2	27.7	47.4	29.2	-14.14	33.18	40.29	23.18
AB	27.5	27.2	43.0	30.5	-15.57	31.63	35.24	24.18

'BA' represents no laser first and with laser second; 'AB' represents with laser first and no laser second; SD: Standard deviation.

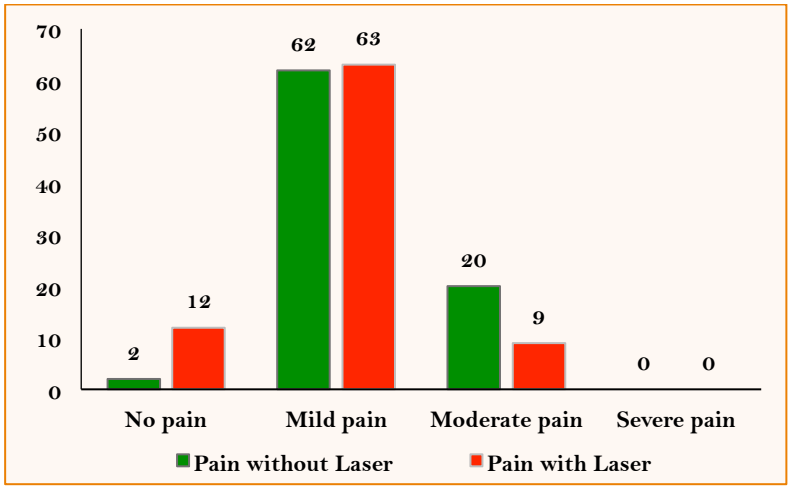

Figure 2. Distribution of pain intensity categorized by injection with and without laser.

Table 2 presents the mean pain scores of male and female patients in use and no use of laser. The mean pain score in the use of laser was significantly lower than that in no use of laser ($p<0.001$). There was no significant difference in pain scores in use and no use of laser in males ($p=0.060$), but females had significantly lower pain scores in use of laser ($p<0.001$). The difference in pain score in the use of laser showed no significance between males and females ($p=0.0272$). However, the pain scores of males and females were significantly different following injection without using a laser ($p=0.005$), and males experienced a significantly lower level of pain than females in no use of laser. The overall pain score (with or without the use of laser) showed no significant difference between males and females ($p=0.108$). No serious harm was observed other than pain after injection.

Table 2. Mean pain scores of male and female patients in use and no use of laser.

Group	Pain with Laser		Pain without Laser		Pain Difference (With Laser - Without Laser)				p-value†
	Mean	SD	Mean	SD	Mean	SD	CI 95% of Mean		
							Lower Bound	Upper Bound	
Overall	30.3	27.5	45.2	29.8	-14.86	32.22	-21.85	-7.86	<0.001
Males	27.1	25.7	36.4	28.8	-9.33	31.62	-19.06	0.41	0.060
Females	33.7	29.1	54.4	28.3	-20.66	32.21	-30.83	-10.49	<0.001
p-value‡	0.272		0.005		0.108				

†Paired Sample T-Test; ‡Independent Sample T-Test for comparison between males and females; SD: Standard deviation.

Discussion

The research hypothesis stated that LLLT reduces the pain during anesthetic injection in the anterior maxilla. The results of the study partially support this hypothesis. Our results showed that LLLT reduces injection pain.

In the current research, the injection was performed at the depth of buccal vestibule between the maxillary central and lateral incisors because this area is the most painful area for injection in the oral cavity and it's a relatively simple injection for administration than other injections [3,26].

In the current research, we preferred the split-mouth design due to its benefits. The split-mouth design can eliminate inter-individual variability for assessing treatments' efficacy, despite the carry-across effect as an inherent disadvantage [27]. In addition, we reduced bias and assured randomization because the carry-across effect was not evident since patients were not aware of the laser side.

The results demonstrated a significant difference in the level of pain experienced with and without LLLT, such that the mean pain score following LLLT was significantly lower than that without LLLT. There are controversies regarding the therapeutic effects of using LLLT to decrease pain [13,16-17,25,28-31]. Similar to our findings, Jagtap et al. indicated that LLLT decreases the pain perception prior to injection of local anesthetics [28]. Amarillas-Escobar et al. [16] evaluated the therapeutic effects of 810 nm continuous-wave laser with 100 mW power and reported that although LLLT with the applied protocol decreased postoperative pain, swelling and trismus, this reduction showed no statistical significance. Jajarm et al. [13] reported that 630 nm diode laser significantly decreased pain score and intensity of lesion. Agha-Hosseini et al. [17] reported improvement in pain score and size of lesion following LLLT with 890 nm wavelength and 0.3 to 0.5 J/cm² dosage, which was consistent with our results. Jovanovic et al. evaluated the LLLT effectiveness for pain relief and reported significant pain reduction in patients who underwent LLLT compared with conventional treatment with zinc oxide eugenol at 5 and 8 days after the intervention [29]. Aimbire et al. [30] discussed that LLLT can significantly inhibit inflammatory processes in a dose-dependent fashion and subsequently decrease acute inflammatory pain. However, they called for further clinical studies on different doses of LLLT to assess its efficacy for resolution of acute pains. Kreisler et al. used an 810 nm GaAlAr laser with 50 mW power for pain relief and reported that patients in laser group experienced a lower level of pain than the control group on the first day after treatment [31]. In contrast, Ghaderi et al. [25] showed that the use of 960 nm low-level GaAlAs laser not only could not decrease pain during infiltration anesthesia injection but also increased it in females. Their results were in contrast to our findings. They used a laser at one side but did not use it for the other. Thus, patients were aware of the use/no use of laser. According to Van Bon et al. [32], the use of a new device creates anxiety in females and according to Okawa et al. [8] and Van Wijk and Makkes [33], anxiety can increase the level of pain experienced during infiltration anesthesia. Whereas, we used laser for both sides with the difference that the laser power was zero for the control side. The difference in the results of studies can be due to no uniform reports on physical and biological variables, like laser type, output power (continuous or pulsed), pulse frequency, wavelength, voltage, density, duration of radiation and used method, source distance from irradiated tissue, histologic tissue differences and absorption features. For these reasons, standardizing and comparison of the results are difficult [11,14].

Since a laser with two wavelengths has not been used for this purpose in previous studies, we used a diode Quick Lase 810-980 nm laser to assess its efficacy and the synergistic or inhibitory effects of the two wavelengths on pain.

The analgesic mechanism of action of laser has not been well understood. However, the optimal efficacy of LLLT for wound healing, resolution of inflammation and pain relief has been reported. LLLT causes vasodilation and increases blood flow, which can enhance healing [34]. Also, mitochondrial stimulation for greater production of reactive oxygen species has been reported following LLLT, which affects the oxidation-reduction reactions and subsequently the inter-cellular homeostasis and cell proliferation [30]. A laser also causes the release of endorphins and enkephalin that decrease conduction and perception of pain [35]. Neural conduction is inhibited by LLLT since it causes structural changes in sodium-potassium channels, which lead to pain relief [36]. According to Deana et al. [37], another mechanism of pain reduction by LLLT is the stimulation of the production of beta-endorphins, which are natural mediators produced by the human body to decrease pain. LLLT also inhibits the release of arachidonic acid; as we know, arachidonic acid induces injured cells to produce metabolites that stimulate pain receptors.

No significant difference was found in the pain level between laser and no laser groups in males, but the difference in this regard was significant in females ($p<0.05$), and female patients experienced a significantly lower level of pain following LLLT. The difference between males and females in pain scores following the use of laser was not significant ($p=0.272$), but males had a significantly lower level of pain during injection without laser ($p=0.005$).

Previous investigations have shown that the correlation between gender and pain is complex and a higher prevalence of pain in females has been reported [38-41]. Although the underlying mechanisms for difference in pain perception between males and females have not yet been fully elucidated [39], it may be due to increased activity of C fibers by capsaicin as a vasomotor in females compared with males [39], the difference in distribution, expression or sensitivity of opioid receptors of the central nervous system in males and females [40], difference in the activity of dopaminergic system in males and females or psychosocial differences between males and females [41].

One of the limitations of the current research was the buccal infiltration method, which was chosen because it is easy to administer, not extremely painful [42], and there is minimal difference in injection by the clinician [42]. In addition, the penetration depth of the needle varies in different injection techniques. This indicates that our findings should not be generalized to more painful palatal injections or mandibular nerve blocks. We suggest future controlled studies will be conducted to compare the effect of the LLLT with various mode on the pain of different injection techniques.

Conclusion

The low-level laser therapy can be successfully used to decrease the level of pain experienced during anterior maxillary infiltration. This study revealed an interesting finding: Laser reduces injection pain for women more than for men. However, further clinical trials are required to find the most appropriate laser settings for maximum pain reduction. Also, the synergistic effects of low-level laser therapy for pain reduction should be evaluated in future studies.

Authors' Contributions

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HB	https://orcid.org/0000-0003-3310-1265	Formal Analysis, Investigation and Data Curation.
MS	https://orcid.org/0000-0003-3885-6640	Methodology, Writing - Original Draft and Writing - Review and Editing.
HRM	https://orcid.org/0000-0001-9351-1499	Conceptualization, Validation, Resources and Project Administration.
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HM	https://orcid.org/0000-0002-9161-8038	Validation, Formal Analysis, Investigation and Funding Acquisition.
AG	https://orcid.org/0000-0002-8167-7632	Conceptualization, Methodology, Writing - Review and Editing and Supervision.

All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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