Influence of postoperative low-level laser therapy on the osseointegration of self-tapping implants in the posterior maxilla: A 6-week split-mouth clinical study

Uticaj postoperativne terapije laserom male snage na oseointegraciju samourezujućih implantata u bočnoj regiji gornje vilice: šestonedeljna split-mouth klinička studija

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Abstract

Background/Aim. Low-level laser therapy (LLLT) has been proven to stimulate bone repair, affecting cellular proliferation, differentiation and adhesion, and has shown a potential to reduce the healing time following implant placement. The aim of this clinical study was to investigate the influence of postoperative LLLT osseointegration and early success of self-tapping implants placed into low-density bone. Methods. Following the split-mouth design, self-tapping implants (n = 44) were inserted in the posterior maxilla of 12 patients. One jaw side randomly received LLLT (test group), while the other side was placebo (control group). For LLLT, a 637 nm gallium-aluminum-arsenide (GaAlAs) laser (Medicolaser 637, Technoline, Belgrade, Serbia) with an output power of 40 mW and continuous wave was used. Low-level laser treatment was performed immediately after the surgery and then repeated every day in the following 7 days. The total irradiation dose per treatment was 6.26 J/cm² per implant. The study outcomes were: implant stability, alkaline phosphatase (ALP) activity and early implant success rate. The follow-up took 6 weeks. Results. Irradiated implants achieved a higher stability compared with controls during the entire follow-up and the difference reached significance in the 5th postoperative week (paired t-test, p = 0.030). The difference in ALP activity between the groups was insignificant in any observation point (paired t-test, p > 0.05). The early implant success rate was 100%, regardless of LLLT usage. Conclusion. LLLT applied daily during the first postoperative week expressed no significant influence on the osseointegration of self-tapping implants placed into low density bone of the posterior maxilla. Placement of self-tapping macro-designed implants into low density bone could be a predictable therapeutic procedure with a high early success rate regardless of LLLT usage.

Key words: dental implants; oral surgical procedures; laser therapy, low-level; bone regeneration; alkaline phosphatase; treatment outcome.

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Introduction

Low-level laser therapy (LLLT) has been used for more than 30 years in the medical field and no adverse effects have been reported. It is defined as red beam or near-infrared laser therapies of low energy density and output power, with wavelengths between 500 and 1,200 nm, that do not increase normal tissue and body temperature. Its effects are therefore nonthermal and biostimulative.

As LLLT affects various tissue responses such as blood flow, inflammation, cellular proliferation and/or differentiation, stimulation with LLLT creates a number of environmental conditions that appeared to have accelerated healing of bone defects in animal models and clinical investigations.

Though the exact mechanism of these effects is not elucidated yet, they are considered to be results of laser irradiation on the cell membrane, mitochondria, DNA and RNA synthesis, collagen synthesis, neovascularization, cell proliferation, and the production of ATP.

In oral implantology, research has been focused on the potential of LLLT to reduce the healing time following implant placement and to improve the potential for bone regeneration.

Previous experimental studies reported that low-level laser treatment stimulated proliferation and differentiation of osteoblasts as well as their bonding to titanium implant. It significantly increased alkaline phosphatase (ALP) activity, which is considered to be a marker of differentiated osteoblasts, in culture and animal models. When applied in the early postoperative period, LLLT lead to an enhancement of the mechanical strenght of bone-implant interface and stimulation of bone matrix production and bone nodule formation.

There are a number of studies suggesting that low-level laser treatment in the early postoperative period after implant placement may lead to a positive clinical effect. As low-density bone (D3 and D4 class of bone, Leckholm & Zarb classification) is usually present in the molar region of the upper jaw, this has proven to be the region of lower success rates of dental implant therapy due to lack of primary stability that can be obtained. Postoperative LLLT might have potential beneficial influence on dental implant treatment in this area, making it more predictable.

The aim of our study was to investigate the influence of postoperative LLLT on osseointegration of self-tapping implants placed into low density bone, by investigating and comparing clinical status – implant stability with the appearance of the marker of alkaline phosphatase in the periimplant crevicular fluid. The second aim was to evaluate early success rate of implants placed into the premolar/molar maxillary region, regarding LLLT.

Methods

The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2002. The protocol was approved by the Ethics Committee of the Faculty of Dentistry, University of Belgrade (No.36/22), and the patients gave their written informed consent. Written patient’s consent was also obtained to publish clinical photographs.

A total of 12 patients (6 males and 6 females) seeking implant therapy for bilateral reconstruction in the posterior maxilla were recruited for this study. All the patients were healthy adults, age 18 or older. The patients were selected in accordance with the following inclusion criteria: sufficient bone volume to receive implants without requiring bone augmentation (reconstruction) procedures and no history of previous tooth extraction in the last six months in the selected area. Exclusion criteria were: 1) systemic: pregnancy or lactation, systemic disease that affects osseointegration, anticoagulant therapy, systemic glucocorticoid therapy, history of radiotherapy in the craniofacial region within last 12 months, smoking habit of more than 10 cigarettes per day and 2) local: acute infection in the mouth, uncontrolled or untreated periodontal disease.

For patients’ selection and treatment planning, panoramic radiographs and 3D computed tomography scans were required, followed by clinical intraoral examination.

Following split mouth design, a total of 44 self-tapping BlueSky® (Bredent, Germany) implants with diameter of 4 mm and length of 10 mm were inserted bilaterally and symmetrically in the posterior maxilla of the selected patients.

Local anesthesia was induced by infiltration with 2% lidocaine hydrochloride and 1: 80 000 adrenaline. After crestal incision and mucoperiosteal flap elevation, preparations of implant recipient sites were performed under cooling with physiological solution, according to the protocol following the manufacturer’s instructions (Bredent, Germany). The speed of 15 rpm with a torque of 35 Ncm was set for insertion of all implants. The implants were allowed to heal transmucosally and sutures were removed after 7 days.

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Postoperatively all the patients were prescribed amoxicillin (1.5 g) or clindamycin (1.8 g) daily, for three days as well as nonsteroidal anti-inflammatory drugs for pain relief. The patients were also given detailed instructions with regard to oral hygiene. No temporary prosthesis was placed during the entire 6-week observation period.

After the surgery, one of the sides of the upper jaw of the patients was randomly (computer-generated random numbers) chosen to receive low-level laser treatment (test group). The other side of the jaw was placebo, without any treatment performed and served as a control (control group).

A 637 nm gallium-aluminum-arsenide (GaAlAs) laser (Medicelaser 637, Technoline, Belgrade, Serbia) with an output power of 40 mW and continuous wave was used. The implant on the chosen side was irradiated intraorally, orthoradially to the implant's longitudinal axis (Figure 1). Low-level laser treatment was performed immediately after the surgery and then repeated every day in the following 7 days. The total irradiation dose per treatment was 6.26 J/cm² per implant.

Evaluation of osseointegration of implants

All assessments of the study outcomes were performed in a double blind manner, since neither patients (due to placebo) or assessors (not involved in LLLT) were aware of treatment allocation.

Resonance frequency analysis (RFA) was performed using the Osstell™ Mentor instrument (Integration Diagnostics, Göteborg, Sweden) by a trained calibrated operator who was unaware of which side would be irradiated. Measurements were recorded immediately after implant insertion and then postoperatively in a weekly manner during the following 6 weeks. A standardized abutment of fixed length (Smartpeg™ Integration Diagnostics, Göteborg, Sweden) was inserted and hand-tightened into each implant. The transducer probe (Osstell™ Mentor Probe) was held so that the probe tip was aimed at the small magnet on top of the Smartpeg™ at a distance of 2–3 mm (Figure 2). It was held still until the instrument beeped and displayed the implant stability quotient (ISQ) value. Each measurement was repeated until the same value was recorded twice, which was accepted as the authentic value. For the post-surgical stability measurements, abutments were removed from the implants.

Evaluation of bone remodeling intensity and osteoblast differentiation

Peri-implant crevicular fluid (PICF) sampling was performed on the postoperative day 7, 14, 21 and 28. To avoid mechanical irritation, blood contamination or stimulation of the PICF, PICF samples were collected before the clinical measurements. Briefly, following the isolation of the sampling area with sterile cotton rolls, supragingival plaque was removed and the sampling site was gently air dried to reduce any contamination with plaque and saliva. Extreme care was taken to minimize the level of mechanical irritation during PICF sampling as this is known to affect the actual fluid volume in a given site. Standardized sterile paper strip (Periopaper® No. 593525, Oraflow Inc, Amityville NY) was placed at the entrance of peri-implant sulcus and pushed until minimal resistance was felt (Figure 3). Sampling time was recorded twice, which was accepted as the authentic value.
standardized as 60 s. Samples with visible blood contaminations were discarded. Paperstrips with PICF from single implants were immediately used for ALP activity determination. A quantity of 20 µl of distilled water was added to each sample. The tubes were vigorously shaken for 1 min and then centrifuged at 2,000 g for 5 min with the strips kept at the collar of the tube in order to completely elute PICF components.

ALP activity was assayed spectrophotometrically with spectrophotometer at 405 nm (Secomam Basic, France). The principle of method is coloured reaction in which ALP hydrolyses p-nitrophenyl phosphate in the presence of magnesium ions to yellow product p-nitrophenol and inorganic phosphate. The reaction of 10 µl of the sample with 500 µl of the working reagent is at 37 °C, and the rate of increase in absorbance is read after 1 min, then in 1 min intervals and finally recorded after 4 minutes at 405 nm. ALP activity is expressed in U, where U (international unit) represents the amount of enzyme that catalyses release of 1 µmol of p-nitrophenol per min at 37 °C. The final results were reported as total ALP activity (U/sample).

Descriptive statistics for implant stability measurements by means of resonance frequency analysis in test (irradiated) and control (non-irradiated) implants at baseline and during six postoperative weeks

| Time     | Side  | $\bar{x}$ ± SD | Med | Min | Max | 95% CI               |
|----------|-------|----------------|-----|-----|-----|---------------------|
| Baseline | test  | 76.00 ± 3.52   | 75.5| 70  | 82  | 74.25–77.75         |
|          | control | 72.89 ± 7.15   | 74.5| 56  | 80  | 69.33–76.45         |
| 1st week | test  | 74.88 ± 3.40   | 75  | 70  | 82  | 73.06–76.69         |
|          | control | 74.69 ± 4.80   | 74.5| 67  | 84  | 72.13–77.24         |
| 2nd week | test  | 74.22 ± 3.93   | 74  | 68  | 81  | 72.27–76.18         |
|          | control | 72.56 ± 5.67   | 72.5| 61  | 80  | 69.74–75.37         |
| 3rd week | test  | 72.67 ± 3.65   | 73  | 61  | 77  | 70.85–74.48         |
|          | control | 70.44 ± 6.16   | 70  | 55  | 80  | 67.38–73.51         |
| 4th week | test  | 72.50 ± 4.18   | 73  | 60  | 77  | 70.42–74.58         |
|          | control | 69.22 ± 9.09   | 70  | 39  | 79  | 64.70–73.74         |
| 5th week | test  | 72.94 ± 3.92   | 73.5| 63  | 79  | 71.00–74.89         |
|          | control | 69.83 ± 7.03   | 71.5| 48  | 78  | 66.34–73.33         |
| 6th week | test  | 72.67 ± 3.69   | 73.5| 63  | 78  | 70.83–74.50         |
|          | control | 70.61 ± 7.20   | 72  | 52  | 79  | 67.03–74.19         |

The results are presented as implant stability quotient values. Statistical analysis was performed using the SPSS® 17.0 software (SPSS Inc., Chicago, IL, USA). Implants were used as units of analysis. ISQ and ALP activity data were reported using measures of central tendency (mean, median) and variation (standard deviation, min, max, 95% confidence interval). One-sample Kolmogorov–Smirnov test was used to assess the normality of data distribution. Repeated measures analysis of variance was performed to analyze changes of ISQ, as well as ALP activity data, during the observation period and was followed by post hoc least significant difference test to determine differences within groups between particular observation points. The statistical significance of differences in the observed parameters (ISQ and ALP activity) between the groups in each observation point was analyzed using paired samples t-test since data from strictly symmetrical positions of the implants were compared (split-mouth design). The statistical significance of all tests was defined as $p < 0.05$.

Results

Twelve eligible patients were enrolled in the study. They received a total of 44 implants. Since all 4 implants of one male patient aged 68 inserted bilaterally into the regions of the first and the second maxillary molars failed to achieve primary stability sufficient for the one-stage surgery approach, they were covered, not irradiated and excluded from the study. Eleven remaining patients of both genders (5 females and 6 males), mean age 61.28 years (55 to 75) enrolled in this study completed the study protocol. They received a total of 40 implants bilaterally inserted into premolar and/or molar maxillary regions, with 20 implants randomly and symmetrically attributed to each of the two groups, irradiated (test) or non-irradiated (control) group that were included in the analyses. A total follow-up period per patient was 6 weeks.

Resonance frequency analysis

Within the test group significant changes were recorded during a 6-week follow-up ($p = 0.016$) (Table 1, Figure 4).

Table 1

| Time     | $\bar{x}$ ± SD | 95% CI       |
|----------|----------------|--------------|
| 1st week | 74.88 ± 3.40   | 73.06–76.69  |
| 2nd week | 74.22 ± 3.93   | 72.27–76.18  |
| 3rd week | 72.67 ± 3.65   | 70.85–74.48  |
| 4th week | 72.50 ± 4.18   | 70.42–74.58  |
| 5th week | 72.94 ± 3.92   | 71.00–74.89  |
| 6th week | 72.67 ± 3.69   | 70.83–74.50  |

The maximum stability was achieved at baseline and afterwards significantly declined in the 2nd, 3rd and 4th week ($p = 0.029$; $p = 0.007$; $p = 0.008$; respectively) with the minimal recorded value in the 4th week. In the 5th week it started to rise insignificantly, but fell again in the 6th week, in both ob-
servation points still being significantly lower than the baseline stability ($p = 0.017$; $p = 0.005$; respectively). The differences in ISQ values between both consecutive weeks within the test group were not significant ($p > 0.05$).

**Fig. 4 – Effect of low-level laser therapy on implant stability measured by resonance frequency analysis.**

In the control group significant changes in implant stability over time were revealed ($p = 0.023$) (Table 1, Figure 4). The maximum implant stability was achieved in the 1st week, and afterwards significantly decreased in the consecutive 2nd and 3rd week ($p = 0.047$; $p = 0.044$; respectively). An insignificant decrease continued in the 4th week ($p = 0.234$), when the minimum value was recorded and was significantly lower than baseline stability ($p = 0.039$). Afterwards it started to rise insignificantly during the 5th and 6th consecutive weeks ($p = 0.401$; $p = 0.110$; respectively) with ISQ values recorded in the 5th week being significantly lower compared to baseline stability ($p = 0.029$) whereas stability recorded in the 6th week was insignificantly different compared to baseline ($p = 0.074$).

Between group comparative analysis revealed higher ISQ values in the test group compared to the controls during the entire 6-week observation period with the difference being statistically significant in the 5th week ($p = 0.030$) (Table 2). The highest implant stability was recorded at baseline, in the test group. Both groups showed the "stability dip" (with the lowest ISQ values) in the 4th week, with the minimal recorded ISQ value in the control group (Figure 4).

**Alkaline-phosphatase activity**

Within the test group, statistically significant changes of ALP activity were observed during the 4-week observation period ($p < 0.0005$) (Table 3, Figure 5). The highest ALP activity was recorded in the 1st week and afterwards significantly decreased in the 2nd week ($p \leq 0.005$). An insignificant decrease continued from the 2nd week till the 3rd week ($p = 0.175$) followed by an insignificant increase recorded in the 4th week ($p = 1.000$). The ALP activity value in each observation point (2nd, 3rd and 4th week) was significantly lower than in the 1st postoperative week ($p \leq 0.0005$; $p \leq 0.0005$; $p = 0.010$; respectively).

**Fig. 5 – Effect of low-level laser therapy on alkaline phosphatase (ALP) activity in peri-implant crevicular fluid, measured spectrophotometrically during a 4-week observation period.**

### Table 2

differences in implant stability between irradiated (test) and non-irradiated (control) implants

| Time      | Implant stability quotient (± SD) | 95% CI for MD    | $p$  |
|-----------|----------------------------------|------------------|------|
| Baseline  | 76.00 ± 3.52                     | 72.89 ± 7.15     | -0.78177 to 7.00399 | 0.110 |
| 1st week  | 74.88 ± 3.40                     | 74.69 ± 4.80     | -3.45378 to 3.82878 | 0.914 |
| 2nd week  | 74.22 ± 3.93                     | 72.56 ± 5.67     | -1.73616 to 5.06950 | 0.316 |
| 3rd week  | 72.67 ± 3.65                     | 70.44 ± 6.16     | -0.88360 to 5.32805 | 0.150 |
| 4th week  | 72.50 ± 4.18                     | 69.22 ± 9.09     | -0.72534 to 7.28089 | 0.102 |
| 5th week  | 72.94 ± 3.92                     | 69.83 ± 7.03     | 0.34554 to 5.87668  | 0.030* |
| 6th week  | 72.67 ± 3.69                     | 70.61 ± 7.20     | -0.60045 to 4.71157 | 0.121 |

MD – mean difference; * $p$ values (paired samples t-test) – statistically significant; CI – confidence interval.

### Table 3

descriptive statistics for alkaline phosphatase activity assayed spectrophotometrically in test (irradiated) and control (non-irradiated) implants during four week observation period

| Time     | Side | Mean ± SD | Med | Min | Max | 95% CI  |
|----------|------|-----------|-----|-----|-----|---------|
| 1st week | test | 21.53 ± 6.65 | 24.47 | 9.87 | 30.13 | 18.22–24.84 |
|          | control | 18.16 ± 5.11 | 17.92 | 9.73 | 26.87 | 15.62–20.71 |
| 2nd week | test | 11.26 ± 4.64 | 10.40 | 4.48 | 17.77 | 8.95–13.57 |
|          | control | 10.39 ± 4.05 | 9.35 | 4.68 | 17.17 | 8.23–12.55 |
| 3rd week | test | 9.36 ± 4.23 | 8.82 | 4.20 | 19.32 | 7.25–11.46 |
|          | control | 10.22 ± 4.26 | 8.50 | 3.08 | 17.92 | 8.03–12.41 |
| 4th week | test | 11.96 ± 8.34 | 8.89 | 5.46 | 39.92 | 7.81–16.10 |
|          | control | 8.45 ± 3.46 | 7.47 | 3.05 | 18.97 | 6.73–10.17 |

The results are presented as U/sample, where U (international unit) represents the amount of enzyme that catalyses release of 1 µmol of p-nitrophenol per min at 37 °C; CI – confidence interval.

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pattern of ALP activity changes over time was different in the test and control groups (Figure 5). After the initial decline of ALP activity in the test group an increase in the 4th week was observed reaching values similar to those of the 2nd week \((p = 1.000)\), whereas in the control group a continuous decrease was recorded.

**Early implant success**

The early implant success rate after the first six weeks (prior to implant placement) was 100\%, regardless of LLLT usage. No adverse event was recorded during the follow-up.

**Discussion**

Osseointegration is an essential prerequisite for the dental implants’ long-term prognosis. Therefore, chemical, biological and biophysical adjunctive therapies to improve and accelerate healing at bone-implant interface have been widely investigated\(^{15}\). This randomized, double blind, split-mouth clinical study was focused on the effect of postoperative LLLT using a 637 nm GaAlAs laser with an output power of 40 mW and total irradiation dose \(\text{per treatment of 6.26 J/cm}^2\text{ per implant, on osseointegration of self-tapping implants placed into low density bone of posterior maxilla.}^{15,23}\)

A 637 nm GaAlAs laser has been chosen due to its beneficial effects on bone regeneration reported in animal\(^3\) and clinical studies\(^4\). LLLT has been found to increase osteoblastic proliferation, collagen deposition, and bone neoformation in the irradiated comparing to non-irradiated bone\(^3,9\). Studies using animal models and human osteoblast-like cells cultures, demonstrated that the use of low-level laser after titanium implant insertion promoted osseointegration due to rapid bone turnover\(^7,12\) and seemed to accelerate active bone replacement without causing tissue or implant damage\(^7\). Histomorphometric evaluation in animal models revealed more bone-implant contact in the irradiated groups as compared to the controls at 3 and 6\(^{17,19}\) and 16 weeks postoperatively\(^20\). These results suggest that LLLT may stimu-

| Time            | ALP (\(\mu\text{g} \text{mg}^{-1}\) – SD) | 95% CI of MD | \(p\)   |
|-----------------|------------------------------------------|--------------|--------|
| 1st week        | 21.53 ± 6.65                            | -0.50252 to 7.24085 | 0.084  |
| 2nd week        | 11.26 ± 4.64                            | -0.26683 to 3.42371 | 0.088  |
| 3rd week        | 9.36 ± 4.23                             | -2.77642 to 1.61913 | 0.584  |
| 4th week        | 11.9 ± 8.54                             | -0.85890 to 7.87234 | 0.108  |

ALP activity is presented in U/L; MD – mean difference; \(p\)-values (paired samples \(t\)-test)

CI – confidence interval.

In this study osseointegration was evaluated through its two indicators – secondary implant stability measured by means of RFA and ALP activity assayed spectrophotometrically. Secondary implant stability is a clinical reflection of cellular events in peri-implant healing department and therefore indicates the rate and extent of osseointegration\(^21\). We used RFA as a non-invasive method that has proved to be a reliable tool to assess implant stability, determine different healing phases of dental implants and predict success of implant treatment\(^21\). Longitudinal ISQ values in both groups followed the usual pattern of changes with "stability dip" in the 4th postoperative week that reflected bone remodeling process when primary spongiosa was being replaced with lamellar and/or parallel-fibered bone\(^16,22\). The trend of higher ISQ values recorded in the test group compared to controls during the entire 6-week period of observation, reached a significant difference in the 5th postoperative week. This result might suggest biomodulatory effect of LLLT that increases cellular activity and bone apposition but still not clinically significant to provide an earlier and better anchorage of implants. Statistically significant regeneration of bone tissue around irradiated implants was recorded in an intermediate period, which was in agreement with literature data\(^13,23\). It has been shown that although LLLT is capable to increase the number of osteogenic cells in the very initial stage of healing, its effect on implant stabilization in this stage is still insignificant\(^13,23\). Conversely, previous reports of animal studies reported that postoperative LLLT improved late bone repair, affecting cellular proliferation, differentia-

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The authors agreed that single 14 or multisession 12, 13 LLLT beneficial effect of LLLT was perhaps masked by high initial when measured by RFA. The authors remarked that potential found of any effect of LLLT on the stability of implants number of cell divisions to express ultimately a mature os-

tiated osteoblasts and their activity, as early progenitor cells do crevicular fluid. ALP is considered to be a marker of differen-

tion in comparison to non-irradiated sites 13, 14. The only clinical study that investigated the stability of oral implants after LLLT was the study of García-Morales et al. 24. Under the conditions of their study, no evidence was found of any effect of LLLT on the stability of implants when measured by RFA. The authors remarked that potential beneficial effect of LLLT was perhaps masked by high initial stability attained in the posterior mandible region 25. With regard to different irradiation protocol used in a García-Morales study 24 (infrared laser with seven irradiations repeated every 48 h for the first 14 days), as well as different implantation sites, comparison with our results is difficult. In our study, during the whole 6-week observation pe-


diobium characteristics of bone-implant interface. 12–14. The authors agreed that single 14 or multisession 12, 13 LLLT was beneficial to improve bone-implant interface strength, resulting in higher values of removal torque required to de-
tach bone and implant in sites previously submitted to irra-
diation in comparison to non-irradiated sites. 13, 14.



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