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ORIGINAL ARTICLE

Superpulsed laser therapy on healing process after tooth extraction in patients waiting for liver transplantation

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Abstract Alveolar healing following tooth extraction is a complex repair process involving different tissues, including epithelium and bone. This research aimed to study the effect of laser therapy on alveolar healing process in patients waiting for liver transplantation, evaluating some inflammation, osteogenesis, and clinical parameters. Twelve patients with hepatic failure waiting for liver transplantation, with indications to bilateral extraction, entered the split-mouth study. One post-extractive defect was treated with laser while the other was left without treatment. Specimens of soft tissues were removed from around the tooth before extraction and after 7 days. Superpulsed laser irradiation prevented IL-1β increase and induced IL-6, IL-10, and collagen III increase at 7 days in comparison to their level before extraction, whereas the other parameters were unmodified. Moreover, the epithelial regeneration evidenced a positive result of laser therapy, and the patients reported less pain in the site treated with laser. In conclusion, laser therapy appears to be the treatment of choice for patients due to its clinical efficacy, safety, good tolerance, and its ability to prevent inflammation.

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Introduction

Alveolar healing following tooth extraction is a complex repair process involving different types of tissues, including epithelium and bone. In healthy subjects, epithelial cells start to migrate early during the first day post-extraction and their proliferation is already marked by day 4; bone production begins at 10 days after extraction [1] and is no longer evident at 20 weeks [2].

Patients with liver disease could have a high risk for post-operative hemorrhages and augmentation of fibrin cloth stabilization time in the first period of healing process, since the liver is responsible for the production of the main coagulation factors [3]. Therefore, it is important to accelerate the wound-healing process in order to reduce healing delay and any possible post-operative complications that may arise.

Synthetic bone substitutes can also be used to accelerate bone repair in tooth extraction; these include various types of hydroxyapatite and synthetic glasses [4]. Since these substitutes especially target bone repair, other techniques could be tested.

Various studies have addressed the application of laser therapy to dental practice [5, 6]. In general, low-level laser therapy (LLLT) has been used for several years, and no adverse effects have been demonstrated [5, 7]. LLLT is thought to reduce pain [8, 9], accelerate wound healing, and reduce the inflammatory process, as well as enhancing bone remodeling and repair [5, 10]. A literature review of studies regarding wound healing in general identified 47 relevant studies in rodents. Findings from these studies consistently

demonstrated the ability of laser or monochromatic light therapy to stimulate wound-healing processes in experimental wounds in rats and mice, which strongly supports the case for further controlled research in humans [11–13].

Regarding healing of bone defects and fractures, and the osseointegration of biomaterial, some studies are available, including those using cell cultures, animal models, and clinical studies. These have reported a positive effect of LLLT on bone healing. The use of LLLT for biostimulation of alveolar bone repair has thus been steadily increasing. As a bone attachment stimulating factor, LLLT could be used by dentists in cases where negative factors are present that are predictive of poor osseointegration; this represents an important improvement in dental practice [5].

Little evidence is available concerning the influence of monochromatic light on either periodontal or peri-implant wound healing derived from experimental animal studies and randomized controlled clinical trials [14] and the benefit over conventional treatment procedures is in doubt. Moreover, no studies concern the use of laser therapy for improving healing processes following tooth extraction in patients with pathological problems, such as those waiting for a liver transplantation.

To examine the effect of laser use in healing processes following tooth extraction, it is appropriate to evaluate some inflammatory and osteogenesis parameters.

Inflammation is a very complex and finely orchestrated process involving many cell types and molecules [15–17]. Among inflammatory factors, inteurleukin-1β (IL-1β), IL-6, and prostaglandin-E2 (PGE2) are factors present in the gingival crevicular fluid involved in the establishment of inflammatory processes in the oral cavity [18, 19], whereas IL-10 and transforming growth factor (TGF)-β2 can be involved in the healing processes.

IL-1β, a strong pro-inflammatory protein, is responsible for the mediation of prostaglandin and leukotriene production and the platelet-activating factor in several cell types, and it also plays a major role in both acute and chronic periodontal inflammation [16, 17, 20]. Moreover, it promotes osteoclast formation and bone resorption [21]. In fact, it has been demonstrated that inhibition of IL-1β reduces tissue destruction and the progression of inflammation in experimental periodontitis [15, 22].

IL-6 has pro- and anti-inflammatory functions and controls regenerative processes including wound healing and liver regeneration [23].

IL-10 is a pleiotropic cytokine that regulates a variety of functions of hemopoietic cells. Its principal everyday function appears to be one of containment, and, eventually, termination of inflammatory responses. Thus, IL-10 facilitates elimination of infectious organisms while causing minimal damage to host tissues. Early clinical trials suggest that IL-10 has a good safety profile and may be of use in treating autoimmune and inflammatory conditions. IL-10 potently inhibits production of several cytokines by activated monocytes/macrophages. Moreover, IL-10 has been found to inhibit production of PGE2 through the down-regulation of COX-2 expression [24].

The present study examines the effects of laser therapy on the healing process following tooth extraction in patients waiting for a liver transplantation, and evaluates inflammation, osteogenesis, and clinical parameters.

Patients and methods

Patients

Twelve patients with hepatic failure waiting for a liver transplantation with indications to bilateral extraction were enrolled in the study. Informed consent was obtained from all patients and the study protocol was approved by the ethics committee of Turin University. This was a split-mouth study where the patient becomes his/her own control, thus eliminating all individual differences in response to laser treatment.

Surgical protocol

Two extractions were performed in the same surgical session. After locoregional anesthesia (mepivacaine 2% with adrenaline 1:100000), tooth extraction was achieved through luxation and avulsion with a clamp. In each patient, one post-extraction site was treated with laser irradiation, while the other was left untreated as the control. The left and right sites were assigned randomly. This provided the best possible control group because both treatments were carried out in the same patient, with the same surgical procedure, and in identical microbiologic conditions, and by the same surgeon. In all cases, 3-0 silk sutures were used to suture the alveolar mucosa, which were removed after 7 days. Patients were given an antibiotic (1 g amoxicillin every 12 h for 6 days) and oral anti-inflammatory treatment (400 mg ibuprofen every 12 h for 3 days), since the patients need this therapy.

Specimens of soft tissue were removed from the control and treated with laser sites at the following times: before tooth extraction (T0) and after 7 days (T7). All specimens were placed in RNA Later solution (Qiagen, Milan, Italy), and maintained at –80°C until use.

Laser treatment

In each patient, one post-extraction site was treated with superpulsed laser irradiation immediately after molar extraction and at days 3 and 5. A Lumix 2 HFPL Dental

device IR (904–910 nm) gallium arsenide laser (Fisioline s. n.c., Verduno, Cuneo, Italy) was used, with the following experimental parameters: pulse width 200 ns, minimum peak power 33 W, average out power 200 mW (measured by absolute measurer), illuminated area 1 cm^2, irradiance 200 mW/cm^2, frequency 30 kHz, exposure time 15 min, total energy 180 J. The dose administered was 180 J/cm^2. The laser probe was placed in contact with the mucosa to cover the alveolar socket without moving. The patient was not aware of the side that was being treated with the laser, since a non-working laser was used for the untreated site. Specimens of soft tissue were removed as above (Fig. 1).

Biological factor analysis

The specimens removed from the control site and from the site treated with laser irradiation were processed to determine expression of inflammatory and osteogenesis parameters, using real-time polymerase chain reaction (PCR). IL-1β, IL-6, IL-10, transforming growth factor (TGF)-β2, cyclooxygenase-2 (COX-2), bone morphogenetics protein (BMP)-4 and BMP-7, peroxisome proliferator-activated receptor (PPAR)-β, and collagen type I and type III were examined.

Total RNA was extracted from the specimens using the NucleoSpin RNA II Kit (Macherey-Nagel GmbH & Co. KG, Düren, Germany). Real-time PCR was performed with single-stranded cDNA prepared from total RNA (1 μg) using the High-Capacity cDNA Archive kit from Applied Biosystems (Foster City, CA).

The forward (FW) and reverse (RV) primers shown in Table 1 were designed using the Beacon Designer® program (Bio-Rad, Hercules, CA). Twenty-five microliters of a PCR mixture containing cDNA template equivalent to 40 ng of total RNA, 5 pmoles each of forward and reverse primers, and 2× IQ SYBR Green SuperMix (Bio-Rad, Hercules, CA) were amplified using an iCycler PCR instrument (Bio-Rad, Hercules, CA) with an initial melt at 95°C for 10 min, followed by 35-40 cycles at 95°C for 40 s, annealing temperature for each primer set for 40 s, and 72°C for 40 s. A final extension of 7 min at 72°C was applied. Each sample was tested in duplicate, and threshold

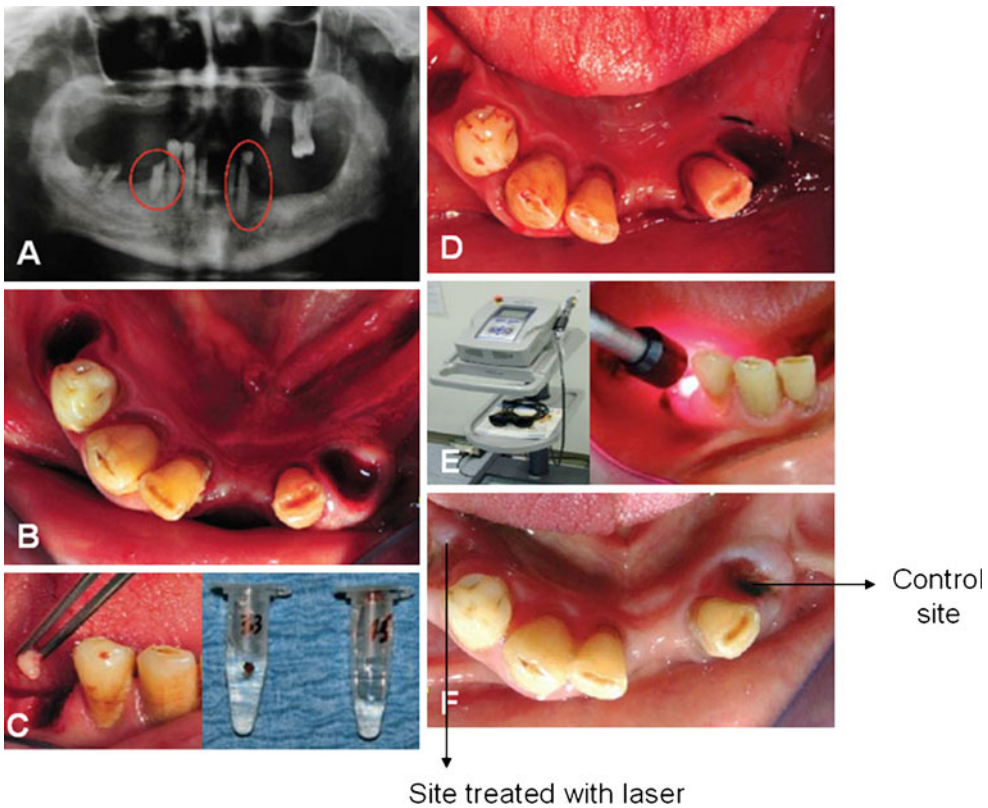

Fig. 1 Case report: protocol of extraction and laser treatment. **a** All patients were referred to undergo a radiological examination that include a dental panoramic radiograph (OPT). **b** Two dental extractions were performed in the same surgical session. **c** Samples of soft tissues were removed from around post-extraction sockets before tooth extraction and after 7 days. All specimens were placed in RNA Later solution (Qiagen, Milan, Italy), and maintained at –80°C until use. **d** 3-0 silk sutures were used to stitch the alveolar mucosa. **e** After teeth extractions, one post-extractive defect was treated with superpulsed laser irradiation, the third and the fifth day after surgery. A Lumix 2 HFPL Dental device IR (904–910 nm) gallium arsenide laser (Fisioline s.n.c., Verduno, Cuneo, Italy) was used. **f** Sutures were removed after 7 days and the degree of epithelial regeneration was evaluated by the surgeon

Table 1 Forward and reverse primers for real-time PCR analysis

Gene Accession no.	Sequence FW (Forward) RV (Reverse)	T annealing # Cycle	Product length
GAPDH	FW 5′- GTC GGA GTC AAC GGA TTT GG-3′	52°C	142 pb
NM_002046	RV 5′- GGG TGG AAT CAT ATT GGA ACA TG-3′	35 X	
IL-1β	FW 5′- GCA CCT TCT TTC CCT TCA TCT TT-3′	52°C	105 pb
AF043335	RV 5′- GCG TGC AGT TCA GTG ATC GTA-3′	40 X	
IL-6	FW 5′- CCA GTA CCC CCA GGA GAA GAT T-3′	52°C	78 pb
M14584	RV 5′- GTC AAT TCG TTC TGA AGA GGT GAG T-3′	40 X	
IL-10	FW 5′-CCG AGA TGC CTT CAG CAG AG-3′	60°C	154 pb
AY029171	RV 5′-CAT CAC CTC CTC CAG GTA AAA CT-3′	30 X	
TGF-β2	FW 5′- GAG TAC TAC GCC AAG GAG GTT TAC A-3′	52°C	104 pb
NM_003238	RV 5′- CGA ACA ATT CTG AAG TAG GGT CTG T-3′	40 X	
PPAR-β	FW 5′- AAA GAA GGC CCG CAG CAT-3′	56°C	170 pb
XM_165760	RV 5′- CTG GAT GTC GTG GAT CAC AAA-3′	40 X	
BMP-4	FW 5′- CTC GCT CTA TGT GGA CTT C-3′	58°C	130 pb
D30751	RV 5′- ATG GTT GGT TGA GTT GAG G-3′	40 X	
BMP-7	FW 5′- GTG GAA CAT GAC AAG GAA T-3′	58°C	65 pb
NM_001719	RV 5′- GAA AGA TCA AAC CGG AAC-3′	40 X	
Collagen type I	FW 5′- GAG GAA ACT GTA AGA AAG G-3′	58°C	150 pb
NM_000089	RV 5′- GTT CCC ACC GAG ACC-3′	35 X	
Collagen type III	FW 5′- ACT CGC CCT CCT AAT GG- 3′	59°C	148 pb
NM_000090	RV 5′- GGC ATG ATT CAC AGA TTC C- 3′	35 X	

cycle (Ct) values were averaged from each reaction. For both specimens derived from the control site and from the site treated with laser irradiation, the change in expression was defined as that detected in the specimen taken at T7 versus that detected at T0, calculated as $2^{-\Delta\Delta Ct}$, where $\Delta Ct = Ct_{sample}$ Ct_{GAPDH} and $\Delta\Delta Ct = \Delta Ct_{T7sample}$ $\Delta Ct_{T0sample}$.

Clinical evaluation

Regarding clinical examinations, the epithelial regeneration was evaluated at each experimental time by the operator (Fig. 1), and each patient was asked to score subjective pain on a 10-cm visual analog scale (VAS), with 0 cm indicating no pain and 10 cm indicating the worst possible pain. Pain was evaluated each day at the same time from 2 h after extraction (T1) to day 7 (T7) post-extraction.

Statistical analysis

Statistical analyses were performed using the InStat3 software package. All data are expressed as means ± SD. The significance of differences between the control and specimens treated with laser irradiation mean values was assessed by the non-parametric Wilcoxon matched-pairs signed-ranks test. Data were considered statistically significant at $p<0.05$.

Results

Biological factor analysis in patients waiting for a liver transplantation

Analysis of biological factors involved in inflammation process and in the healing after tooth extraction is shown in Figs. 2, 3, and 4. Figure 2 shows the inflammatory factors,

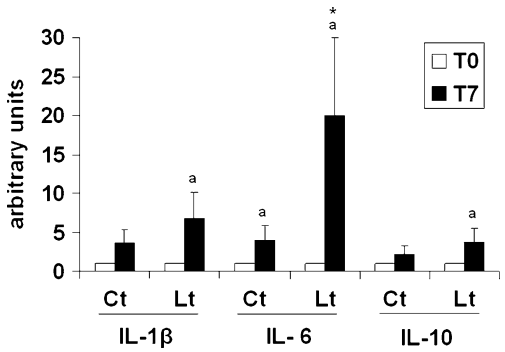

Fig. 2 Expression of IL-1β, IL-6, and IL-10 in the specimens of soft tissues removed from the alveolar site untreated (control) and treated with superpulsed laser irradiation at T7 in patients waiting for a liver transplantation. Control (*Ct*) and superpulsed laser irradiation (*Lt*) values at T7 are referred to their respective T0 values, taken as 1 (*white bar*). The values are means ± SD of 12 patients. The significance of differences between Ct and Lt means was assessed by non-parametric Wilcoxon test. * $p<0.05$ Lt versus Ct, a $p<0.05$ T7 versus T0

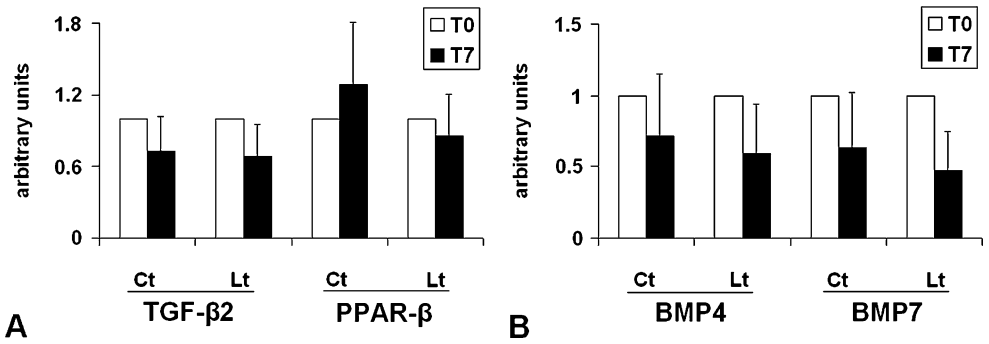

Fig. 3 Expression of TGF-β2, and PPAR-β (**a**), and of BMP-4 and BMP-7 (**b**) in the specimens of soft tissues removed from the site untreated (control) and treated with superpulsed laser irradiation at T7 in patients waiting liver transplantation. Control (*Ct*) and superpulsed laser irradiation (*Lt*) values at T7 are referred to their respective T0 values, taken as 1 (*white bar*). The values are means ± SD of 12 patients. The significance of differences between Ct and Lt means was assessed by non-parametric Wilcoxon test. * $p<0.05$ L versus C, a $p<0.05$ T7 versus T0

namely IL-1β, IL-6, and IL-10. At 7 days from the surgical procedure, in the specimens of soft tissues removed from the sites treated with superpulsed laser irradiation, the values of IL-1β and IL-10 were not statistically different from control specimens, whereas IL-6 increased significantly. Comparing the values of cytokines between T7 and T0, it was observed that IL-1β and IL-10 increased significantly in the specimens treated with laser irradiation and not in the control, whereas IL-6 increased in both control and in the specimens treated with laser irradiation. Figure 3a shows that the two biological factors involved in the healing process, TGF-β2 and PPAR-β, did not show any variation. Figure 3b reports the biological factors involved in the bone healing, BMP4 and 7. These factors showed no variation, probably because 7 days is a very short time to evidence bone healing. Regarding collagen, significant modification was evident for collagen III in the specimens removed at T7 from the sites treated with laser irradiation in comparison to those at T0, and a trend of increase was present in the same specimens removed from sites treated with laser irradiation in comparison to controls (Fig. 4). On the contrary, significant modification was not evident for collagen I (Fig. 4).

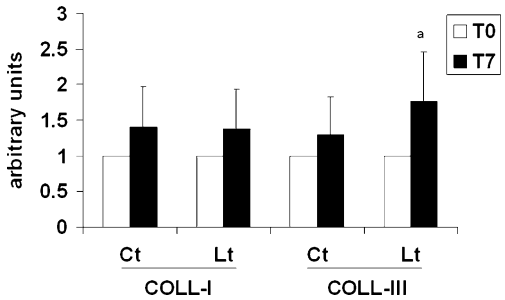

Fig. 4 Expression of collagen I (COLL-I) and collagen III (COLL-III) in the specimens of soft tissues removed from the site untreated (control) and treated with superpulsed laser irradiation at T7 in patients waiting liver transplantation. Control (Ct) and superpulsed laser irradiation (Lt) values at T7 are referred to their respective T0 values, taken as 1 (*white bar*). The values are means ± SD of 12 patients. The significance of differences between Ct and Lt means was assessed by non-parametric Wilcoxon test. * $p<0.05$ L versus C, a $p<0.05$ T7 versus T0

Clinical evaluation in patients waiting liver transplantation

For the clinical examination, at 7 days the operator observed that the process of epithelial regeneration appeared to be more rapid (complete) in laser-treated sites in comparison to control sites (Fig. 1f). The patients were asked to score their feeling of pain on a 10-cm visual analog scale (VAS), with 0 cm reflecting no pain and 10 cm reflecting worst pain possible, and reported less pain at the site treated with laser irradiation than they did at the control site (Fig. 5).

Discussion

This research comprises the first split-mouth study of the effect of laser irradiation on tooth-extraction site healing.

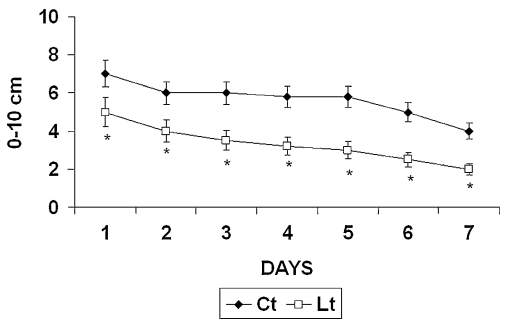

Fig. 5 Visual analog scale (VAS) for pain measurement in untreated (*Ct*) and treated with superpulsed laser irradiation (*Lt*) sites for patients waiting for a liver transplantation. Values are means ± SD of 12 patients. The significance of differences between Ct and Lt means was assessed by non-parametric Wilcoxon test. * $p<0.05$ L versus C

The patient becomes his/her own control, which eliminates all individual differences in response to laser treatment.

This is also the first study examining the healing process following tooth extraction in patients waiting for a liver transplantation, evaluating biological factors rather than simply clinical aspects. Since in these patients, before the transplantation, it is necessary to eliminate each potential infective focus, each not healthy tooth must to be removed [3]. To improve healing and reduce pain are important goals for the patients.

These two points combine to make the study unique of its kind, and it offers significant information for future research on patients with other pathological conditions.

The number of patients is limited to 12, because the number of patients, waiting for liver transplantation and having indication for bilateral extraction, was not very high. Moreover, the patients had to receive antibiotic and anti-inflammatory therapy, however, these drugs did not influence the results, being both sites, treated or not with laser, exposed to drugs.

Laser treatment is an innovative approach, and it is increasingly being used in medicine. It has been shown to produce several different beneficial effects, including pain relief, wound healing, and nerve regeneration. It also has potential antimicrobial and biostimulating effects when applied to oral tissues, for example in improving wound healing, enhancing epithelization after periodontal surgery, minimizing edema after third-molar surgery, and preventing oral mucositis [25–30].

It has been demonstrated that laser therapy stimulates cell proliferation and the formation of lymphatic and blood vessels [31, 32], and it may improve bone mineralization [10, 33, 34]. The effect of laser therapy on bone regeneration has been the focus of recent research, including in dentistry. Studies have investigated the ability of this irradiation to stimulate both bone production and bone-implant interaction [10, 35].

Regarding the biological factors involved in the healing process following tooth extraction, these factors will be analyzed in the specimens of soft tissues removed from the sites treated or not with superpulsed laser irradiation. The majority of the papers regarding oral problems evaluated the content of cytokines in the crevicular fluid [16, 18, 20], whereas, here the ability of the mucosa cells to synthesize the cytokines involved in the inflammatory process and the factors involved in the osteogenesis has been evaluated.

The superpulsed laser irradiation used in this research acts on pro-inflammatory cytokines, preventing the increase of level of IL-1β, but not that of IL-6.

This unexpected result can be explained with two possible explanations, as also reported in a previous paper for the treatment with PRGF to favor the healing wound [36]: (1) IL-6 could facilitate wound healing, because it also shows slight anti-inflammatory activity [37], inducing keratinocyte proliferation and inhibiting pro-inflammatory cytokines [38]. Thus, the involvement of IL-6 in facilitating wound healing must be also considered as a possibility, based on their stimulation of keratinocyte proliferation. It has also been evidenced that IL-6 favors liver regeneration [23]. (2) At the laser-treatment sites, the increase of IL-6 was also accompanied by an increase in IL-10, a cytokine possessing anti-inflammatory activity [39]. Therefore, IL-10 can counterbalance the pro-inflammatory properties of IL-6, favoring the healing process.

Regarding the other parameters evaluated in this research involved in healing process and in osteogenesis, only collagen III was found increased at T7 in the specimens from sites treated with laser. For the other osteogenesis parameters, the observation time was probably too short, and specimens of the mucosa from the healing site would need to be taken on the subsequent days. Differently, the observation of epithelial regeneration evidenced a positive result of laser therapy also in the early times.

The clinical parameter of pain was reported by patients to be lesser at the site treated with laser therapy than at the control site. Since the patient was not aware of the side that was being treated with the laser because a non-working laser was used for the untreated site, the different sensation of the pain was valid.

Our findings might have a significant clinical impact, since laser treatment is easy to perform, does not increase morbidity, and has no side-effects. Moreover, the results obtained from this research may stimulate the use of laser treatment for patients with systemic diseases that may not be compatible with drug treatment.

In conclusion, this study suggests that superpulsed laser irradiation currently appears to be the treatment of choice due to its clinical efficacy, safety, and good tolerance, especially for those patients who require conservative treatment.

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