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Supportive pain management with super-pulsed low-level laser therapy of patients with medication related osteonecrosis of the jaw: clinical trial.

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Abstract

The aim of this study is to share our experience in the application of Low-Level Laser Therapy (LLLT) coupled with the conventional treatment protocol as a supportive pain management modality on a large scale of patients with Medication Related Osteonecrosis of the Jaw (MRONJ) with a history of anti-resorptive administration (Bisphosphonates or Denosumab). This would be through pain evaluation before and after laser application.

Materials and Methods: 25 positive MRONJ patients, after improving their oral health conditions and starting of antibiotics (Amoxicillin + Clavulanic acid and Metronidazole), were exposed to a double diode laser (650nm and 904–910nm, with spot diameter = 8mm), with total energy = 34.8J, for 11 minutes five times over a period of two weeks, in scanning mode at ~1mm. The related pain was observed using a Numeric Rating Scale (NRS) before and after laser application.

Results: A significant decrease of pain was observed in all the cases. 88% of the cases were with NRS values less than 4 points at the end of the study. A statistically significant difference has been recorded for the reported pain ($p<0.0001$).

Discussion: The management objectives of MRONJ are alleviation of pain, control of infection and prevention of osteonecrosis progression. Till now, there is no definitive standard of care for MRONJ patients. LLLT was introduced as a valid modality of pain management in MRONJ patients coupled with the conventional treatment protocols.

Conclusion: The results of this study were like those obtained by other sets of investigators. Further investigations are needed with taking in consideration the size of lesions, other patient data, the presence of controlled and placebo group to establish results that confirm the validity of LLLT as a supportive pain management modality, and finally the exact laser parameters for each case.

Keywords: *Medication Related Osteonecrosis of the Jaw, American Association of Oral and Maxillofacial Surgeons, Bisphosphonates, Low Level Laser Therapy.*

Introduction

The Medication Related Osteonecrosis of the Jaw (MRONJ) has many definitions that were proposed as a trial to differentiate between it and other delayed healing conditions. The most acceptable definition, in the literature, is of the American Association of Oral and Maxillofacial Surgeons (AAOMS) in their last updated position paper [1]. AAOMS considered the establishment of MRONJ in case of existence of all the following criteria; 1) current or previous treatment with anti-angiogenic and/or anti-resorptive agents, 2) clinically exposed bone or bone that can be reached through intraoral or extraoral fistula persisted more than 8 weeks,

and 3) absence of history of radiotherapy or metastatic disease to the jaws [1].
Although it is more than 10 years since the first description of MRONJ by R.E.Marx, [2] the pathogenesis hasn't been fully understood [3].

Many Hypothesis were proposed to explain the unique localisation of osteonecrosis to the jaws such as; altered bone remodelling, [4-5] angiogenesis inhibition, [6] constant micro-trauma, [7] suppression of innate or acquired immunity, [8,9,10] soft tissue Bisphosphonates (BPs) toxicity [11] and inflammation / infection [3,12].

Other authors suggested considering MRONJ as a multi-factorial complication rather than explaining it by a single pathophysiologic mechanism [13].
The AAOMS, in their recent position paper, recommended the prevention of MRONJ as the best approach which can be achieved through a multidisciplinary approach and cooperation between dental and medical professions before the start of BPs therapy, as an attempt to decrease the incidence of MRONJ [3].

The management of established MRONJ is still controversial [3]. Alleviation of pain, infection control, and prevention of osteonecrosis progression are the most acceptable treatment strategy till now and can be achieved through oral antimicrobial rinses, antibiotic therapy and conservative surgical interventions which can be considered only in advanced cases (stage II and stage III) to reduce the volume of colonised necrotic bone [3].

For these reasons, many adjunctive modalities were introduced to combine the non-surgical and surgical management of MRONJ such as; hyperbaric oxygen therapy, [14] platelet rich plasma, parathyroid hormone, [5] bone morphogenic protein, Ozone therapy [15] and Low-Level Laser Therapy (LLLT), however, none of them has been fully proven [3].

LLLT, as one of the innovative approaches in dentistry, has been introduced as a supportive modality to achieve many positive effects such as; pain relief, enhancement of wound healing, [16] enhancement of epithelization after periodontal surgery, [17] minimization of oedema after third molar surgery, [18] prevention of oral mucositis, [19] stimulation of cells proliferation and blood vessels formation, [20] etc.

These positive effects pushed the researchers to exploit LLLT in the management of MRONJ and its related pain as a possible supportive pain management modality [21].

The aim of this study is to share our experience in the application of LLLT coupled with the conventional treatment protocol as a supportive pain management modality on a large scale of patients with positive MRONJ with a history of anti-resorptive administration (BPs or Denosumab). This would be through pain evaluation before and after laser application. According to the results, we will develop our study to a controlled clinical study (with placebo and control group).

Materials and Methods

Twenty-five patients (15 female and 10 males), with a mean age of 71 years suffering from MRONJ, were referred to the Department of Oral Sciences and Maxillofacial Surgery at Sapienza University of Rome.
18 patients have had a history of administration of BPs for bone metastasis (lung, breast and prostate cancer), and 5 patients with multiple myeloma. The remaining 2 patients were as follow; one with anti-resorptive (Denosumab®) administration history for osteoporosis and the other received BPs (Alendronate) for severe osteoporosis.

The medical history and dental history was obtained by a custom–made questionnaire. The questionnaire recorded previous extractions, the presence of removable prosthesis, features of the lesions, and the type and cause of anti-resorptive medications administration for each patient.

An approval from the local Ethics Committee was obtained for this therapeutic approach. A complete clinical examination consisting of chief complaint, extra and intraoral examination was performed for each patient **(Table 1).**

Table 1: patient overview

Patient	Gender	Primary disease	Type of BPs	Site of MRONJ	Stage
1	F	Ca. Lung	Zolendronate	Mandible	I
2	F	Breast Ca.	Zolendronate	Mandible	I
3	F	Breast Ca.	Zolendronate, Pamidronate	Mandible, Maxilla	II
4	F	Breast Ca.	Zolendronate	Mandible	II
5	M	Ca. Prostate	Zolendronate	Mandible	II
6	M	Ca. Prostate	Zolendronate	Mandible	II
7	F	Osteoporosis	Alendronate	Mandible	II
8	M	Multiple Myeloma	Zolendronate	Maxilla	II
9	F	Multiple Myeloma	Zolendronate	Mandible	I
10	F	Multiple Myeloma	Zolendronate	Mandible	II
11	M	Multiple Myeloma	Zolendronate	Mandible	II
12	M	Ca. Prostate	Zolendronate	Mandible	II
13	F	Osteoporosis, Breast Ca.	Alendronate	Mandible	I
14	F	Breast Ca., Diffused bone metastasis	Zolendronate	Mandible	I
15	M	Hypertension, RGE, Hernia, Ca. Prostate	Zolendronate	Mandible	II
16	F	Breast Ca., Diffused bone metastasis	Zolendronate	Maxilla	I
17	F	Multiple Sclerosis, Osteoporosis	Alendronate	Mandible	II
18	F	Breast Ca.	Zolendronate	Mandible	II
19	M	Ca. Lung, Diabetes	Zolendronate	Maxilla	I
20	M	Ca. Lung,	Zolendronate	Mandible	II
21	M	Multiple Myeloma	Zolendronate	Mandible	II
22	F	Osteoporosis, Hypothyroidism	Denosumab	Mandible	II
23	M	Ca. Prostate, Multiple metastases	Zolendronate	Mandible	I
24	F	Breast Ca.	Zolendronate	Mandible	II
25	F	Breast Ca, Bone metastases, Diabetes	Zolendronate	Mandible	II

All the cases were photographed with the same equipment (Nikon D200, Nikon Corporation, Tokyo, Japan) before treatment and compared with analogous pictures after therapy.

Radiographic examinations (Panorama and CT scan) were used for determining the extent of bone necrosis for each case.

Patients experiencing pain in the necrotic areas were recruited for the LLLT protocol after an informed consent has been signed. Patients who refused to stop administration of analgesics during the study were excluded.

Most of the lesions were in the mandible (21 cases) **(Fig. 1)**, three cases were in the maxilla **(Fig. 2)**, and only one patient had an osteonecrosis in both maxilla and mandible.

Fig.1: MRONJ in the mandible

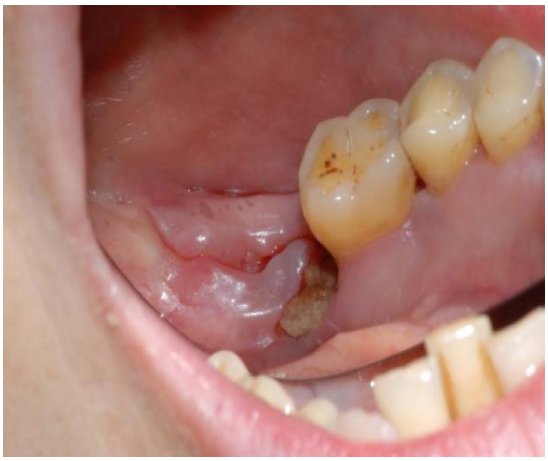
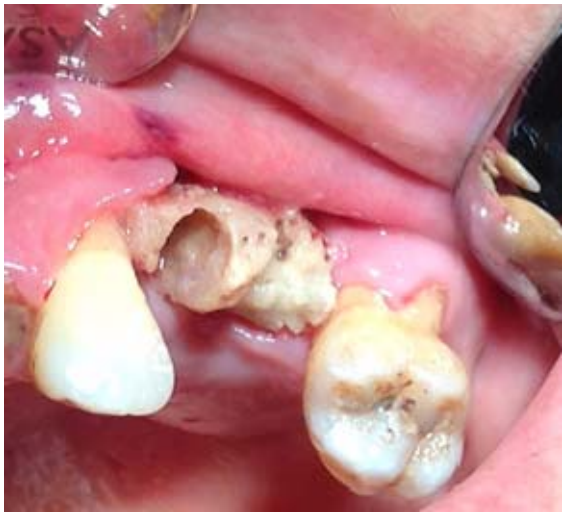


Fig.2: MRONJ in the maxilla



Oral health conditions were improved through many procedures such as; smoothening of the exposed bone irregularities if present by means of a hand-piece with stainless steel bur, removing or attenuating causal agents such as residual roots margins using a diamond bur; performing endodontic treatment, in order to prevent further progress of the lesion, rinsing the necrotic site with a buffered saline solution; applying iodoform gauze, performing professional oral hygiene, and giving the most precise oral care instructions and education about the nature of the disease.

A 0.2% Chlorhexidine mouthwash (Dentosan®, Pfizer Consumer Health Care, Rome, Italy) was prescribed for the first 2 weeks, three times a day, and afterwards, a 0.12% Chlorhexidine mouthwash (Dentosan®, Pfizer Consumer Health Care, Rome, Italy) was prescribed for all the cases.

Amoxicillin + Clavulanic acid (Augmentin®, GlaxoSmithKline S.p.A., Verona, Italy) 1 gr. twice daily for 15 days and Metronidazole 250 mg (Flagyl®, Zambon Italia S.r.l) twice daily for 15 days were prescribed.

A super-pulsed double Diode laser device (Lumix2®; FISIOLINE, Verduno, Italy) with 2 wavelengths 650 nm and 904–910 nm was used in our protocol. The average output power of the visible GaAs source was 100 mW (at the source) with a continuous mode. While, a super-pulsed emission mode (50 kHz) of the infrared GaAs source with a peak power of 45 W and average power of 500 mW, with a pulse duration of 200 n sec.

The painful areas were irradiated with the laser beam (spot diameter = 8mm) using a slow and continuous scanning mode, in a non-contact mode, at ~ 1 cm of distance. The therapeutic cycle consists of five sessions twice weekly, with parameters as follow: Total energy = 34.8 J, the Total application time of 11 mins (2 phases of 5 minutes with an interval of 60 sec). These parameters selected according to the manufacturer's software settings that were listed in the device for the "analgesic" program.

The irradiated area for each case couldn't be estimated, because of the difference in lesions size and the scanning application mode.

The Numeric Rating Scale (NRS) was utilised to measure the pain intensity for each patient twice for each LLLT cycle, once before the initial laser application (T0), and again 3 days after the last laser application (Tend) by different operators. **(Table 2)**.

Monthly follow-up visits were carried out for the first 6 months, and then a follow-up visit every 3 months.

The recorded NRS values before and after the laser application were used for the statistical analysis using the repeated measures one-way ANOVA model (GraphPadPrism7) and the Wilcoxon matched-pairs signed rank test.

Table 2: numeric rating scale (nrs) scores before the first laser application (t0) and after last laser application (Tend)

Patient	First Application T0	Last Application Tend
1	4,5	2
2	6	1
3	5	1
4	6	1
5	10	2.5
6	6	1
7	5	2
8	5	1
9	6	2
10	5	2
11	8	4
12	4	1.5
13	7	3
14	6	1
15	8	5
16	5	1
17	6	2
18	8	3
19	5	1
20	6,5	1
21	7	2
22	8	2
23	7,5	1.5
24	6	0
25	8	4

Results

The Wilcoxon matched-pairs signed rank test revealed a significance. The significant differences were found between NRS scores T0 and Tend ($p<0.0001$).

The average NRS score of T0 was 6.34 (range 4-10), while the average NRS score of Tend was 1.9 (range 0-5). The regression model was not used for the statistical analysis because it works only on large samples and the measurement error for independent variables increases for small samples.

A significant decrease of pain (more than 2 NRS values) was recorded in all the cases. Interestingly, six cases were with NRS scores at T0 from 8-10, two of them (about 8 %) showed NRS scores at Tend between 0-2 (almost without any kind of discomfort). The other four cases showed improvement of pain level with NRS values of 2 to 5 **(Fig. 3, 4)**.

At the end of the study, 88% of all the cases (22 of all the cases) were with NRS values less than 4 points. Overall, there was no case showed worsening of the situation through the study. The mean reduction value was 4.44 for the 25 patients.

The medium pain decrease in females was 4.3 (2.5 – 6) and in males was 4.65 (2.5 – 7.5).

According to the site of MRONJ, our results were quietly similar to the literature, as MRONJ in the mandible is more prevalent than in the maxilla. 21 lesions were in the mandible (84%). The remainder was distributed as follow; three cases in maxilla, and one case in both mandible and maxilla.

17 cases (about 68% of all cases) were suffering from stage II, while 8 cases were suffering from stage I. The average of T0 in stage I was 5.88 (range 4.5-7.5); while in stage II, the average of T0 was 6.56 (range 4-10). On the other hand, the average of Tend in stage I was 1.56 (range 1-3), while in stage II, the average of Tend was 2.1 (range 0-5).

Female patients (about 60%) were more than male patients, which is concordant with literature. As, the higher prevalence of this complication is in female which was explained to be a reflection of the underlying diseases (e.g. osteoporosis, breast cancer) [1].

Discussion

The LLLT can be achieved by the application of laser with a specific wavelength within the therapeutic window in the electromagnetic spectrum, which ranges from 600 nm to 1400 nm, with a range of power from 10-3 to 10-1 W, frequency from 0 Hz (continuous) to 5000 Hz (pulsed), total time from 10 Sec to 3000 Sec and fluence from 10-3 to 10 J/cm2 [21].

Several positive effects of LLLT have been demonstrated in many in-vitro and in-vivo studies such as; reduction of edema and inflammatory cells migration, [22] stimulation of fibroblast proliferation without impairing pro-collagen synthesis, [23] antimicrobial effect through the reduction of S. aureus growth, [24] increase of bone volume and mineral apposition rate, [25] and analgesic effect [26].

The analgesic effect was explained to be a result of releasing neurotransmitters like serotonin, promoting the release of endorphins, increasing mitochondrial ATP production, or due to the anti-inflammatory effect [26]. In addition, Hagiwara S. et al., [26] suggested being also a result of enhancing peripheral endogenous opioid production.

LLLT was introduced as a supportive analgesic modality in many studies for many pathological conditions such as; myo-facial pain dysfunction syndrome, burning mouth syndrome, [31] rheumatoid arthritis, and carpel tunnel syndrome [21].

Several treatment protocols of MRONJ have been proposed such as; nonsurgical protocol with the administration of long-term antibiotics, early conservative surgical approach or extensive and radical surgical resections, however, none of them have been fully proved. Prevention, alleviation of pain and infection control remained the only accepted objectives for the management of MRONJ [21, 27].

From this point, LLLT application with its advantages could be a good modality to be applied with other conservative proposed protocols as a trial to achieve the agreed treatment objectives.

Several studies [28, 29, 21] demonstrated a statistically significant decrease in pain, clinical size, oedema, pus and fistulas after the application of LLLT on established or at risk MRONJ patients. Also, the Nd: YAG (1064 nm) laser was also utilised with its bio-stimulation effect on MRONJ and gave promising results in combination with medical and surgical treatment [30].

Romeo et al., [21] found that LLLT is a valid technique to support the treatment of MRONJ related pain, and suggested the application of LLLT with conventional protocols for MRONJ patients with critical general health conditions or with contraindication of surgical approach.

Through the data analysis, the results of this study are similar to those obtained by other sets of investigators, whereas the average pain reduction was 4.5 points in the NRS scale. Minimum reported reduction was 2.5 points and the maximum one was 7.5.

One of the crucial points of LLLT, that we faced in this study, was estimating the right applied amount of energy, because of presence of many physical and biological variables such as type of laser, output power, frequency of

pulse, fluence, time of application, distance of source from the irradiated tissue, and histological differences between treated tissues [29]. Thus, we followed the recommendation of customising the amount of energy for each case [21].

Fig.3: NRS pre- and post-treatment values – Female patients

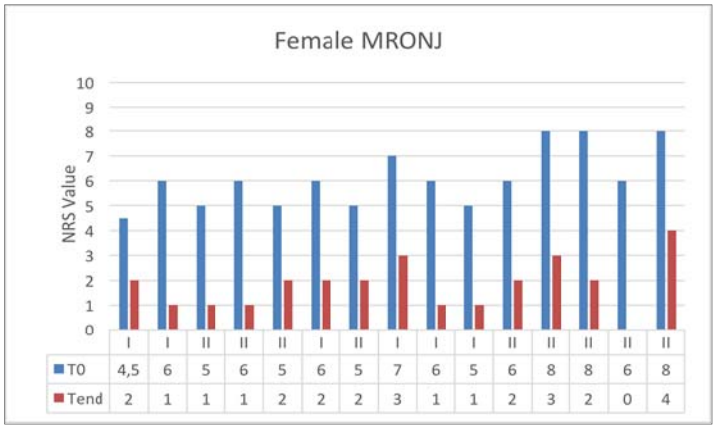
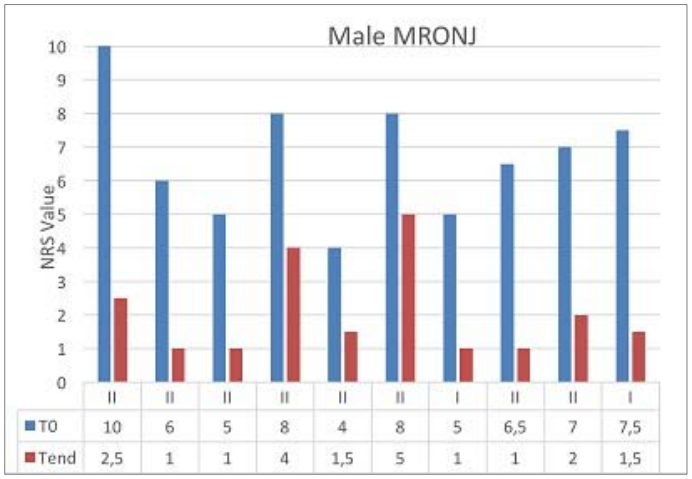


Fig.4: NRS pre- and post-treatment values – Male patients



Conclusion

Till now, preventive measures and supportive conservative protocols are the management strategy of choice. The positive effects of LLLT on healing and remission of pain allowed performing a non-invasive treatment at different stages of the disease without provoking side effects, especially in patients who their medical condition didn't permit the surgical intervention [21].

This study is a supplement to our previous study [21] and its results were promising. Further investigations are needed with taking in consideration the size of lesions, other patient data, the presence of controlled and placebo group to establish results that confirm the validity of LLLT as a supportive pain management modality, and finally the exact laser parameters for each case [21].

Declarations

Consent for publication

Written informed consent was obtained from all the patients.

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There are no funds for this study.

Authors' contributions

All the authors contributed to the workup of this study and the manuscript has been reviewed and approved by all the authors.

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