OSTEONECROSI DELLE OSSA MASCELLARI (ONJ) DA BIFOSFONATI E ALTRI FARMACI: PREVENZIONE, DIAGNOSI, FARMACOVIGILANZA, TRATTAMENTO - UPDATE 2014

Alessandria, sabato 10 maggio 2014

Associazione Cultura e Sviluppo

Piazza Fabrizio De Andrè, Alessandria

Trattamento della ONJ: update della letteratura. Laser e altre terapie

Umberto Romeo

10 Maggio 2014, Alessandria

EUROPEAN MASTER DEGREE: ORAL LASER APPLICATIONS

Bisphosphonate-induced osteonecrosis of the jaw: a medical enigma?

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Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:e1-e8

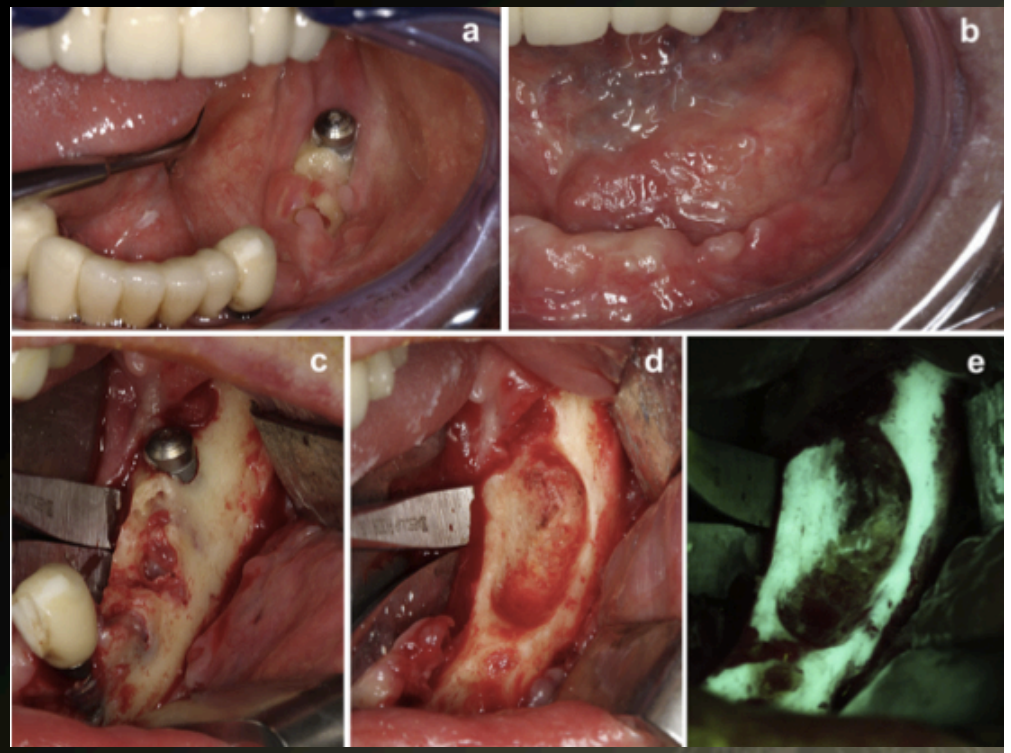
To date, most of the evidence in the management of BION is based on isolated case reports and clinical opinions rather than well-controlled clinical trials from which sound treatment recommendations can be formulated. It concluded that prevention of BION is the best approach and coordination of medical and dental care is important in the establishment of measures aimed at preventing the development of BION of the jaw.

Management strategies

- Laser
- Other therapies:
  - Surgical Management of ONJ (Fluorescence guided bone resection, Platelet-Rich Plasma, Bone Marrow Stem Cell)
  - Teraparatide Hormone
  - Oxygen hyperbaric therapy
  - Ozone Therapy

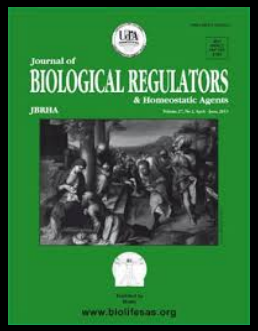
Fluorescence guided bone resection

Otto S et al. "***Successful surgical management of osteonecrosis of the jaw due to RANK-ligand inhibitor treatment using fluorescence guided bone resection***". Journal of Cranio-Maxillo-Facial Surgery 41 (2013)694-698



Fluorescence guided bone resection is suggested as a promising technique for attaining necrotic free bone margins intraoperatively in the management of osteonecrosis of the jaw associated with RANKL-inhibitor treatment […] together with a good antibiotic regimen

Platelet-Rich Plasma (PRP)



Coviello V. et al "***Platelet-Rich Plasma improves wound healing in multiple myeloma bisphosphonate-associated osteonecrosis of the jaw patients***". Journal of Biological Regulators and Homeostatic Agents, Vol 26, n. 1, 151-155 (2012)

Group A

Standard surgical therapy of debridement and sequestrectomy

Group B

Patients received additional autologous PRP

[…] The use of PRP in ONJ MM patients seems to be a good treatment alternative to foster osteogenesis and accelerate wound healing.

"The mechanism of PRP is not fully understood. High concentrations of specific growth factors may be responsible for the beneficial effects in soft and hard tissue wound healing. PRP may enhance the production of high platelet concentration therefore promoting wound healing."

Bone Marrow Stem Cells (BMSC)

Cella L. et al "***Autologous bone marrow stem cell intralesional transplatation repairing bisphosphonate related osteonecrosis of the jaw***". Head and Face Medicine 2011, 7: 16

Stage III - BRONJ

Surgical toilet of the bone lesion → Injection in the lesion of fibrina sponge + 4ml of stem cells suspension + 1ml of PRP

Resolution of symptoms and improved lesion with a pink coloured layer

"Based on chemokine/chemokine-receptor interactions and adhesion molecules, MSCs are potentially capable on finding the site of injury and when, given intravenously, of restoring damaged tissue on site due to their plasticity and/or paracrine properties […] a direct approach, bringing direct into the osteonecrotic site a significant amount of bone marrow enriched in mononuclear cells, could allow a better osteogenesis of the damaged bone based on evidence data of the presence in this cell-fraction of osteoid and angiogenic precursors"

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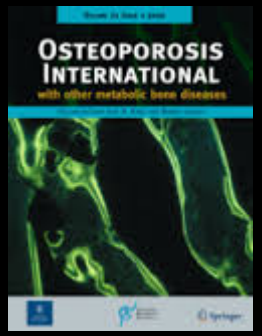
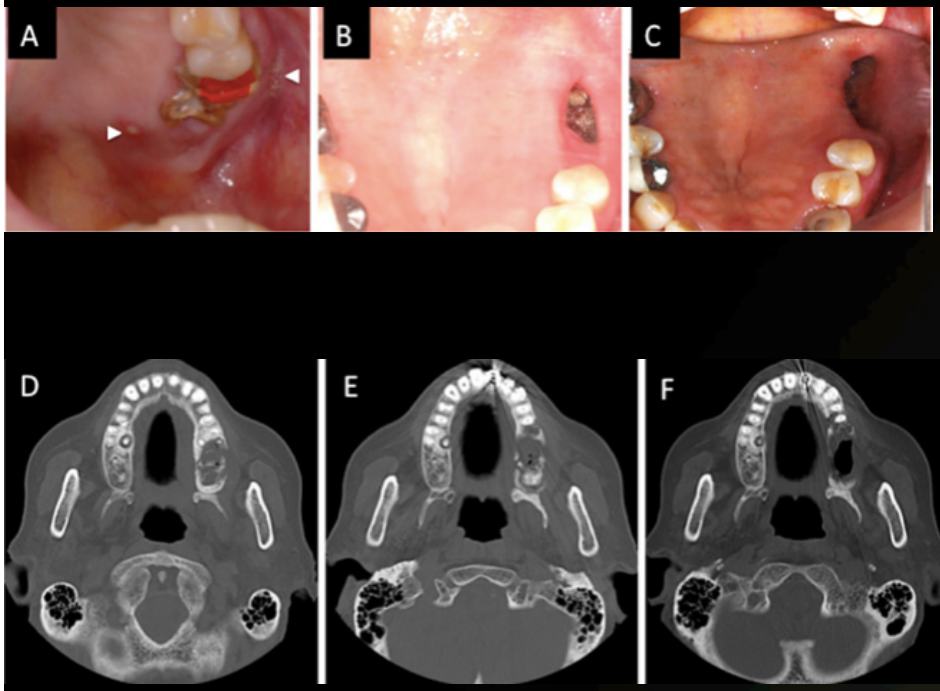
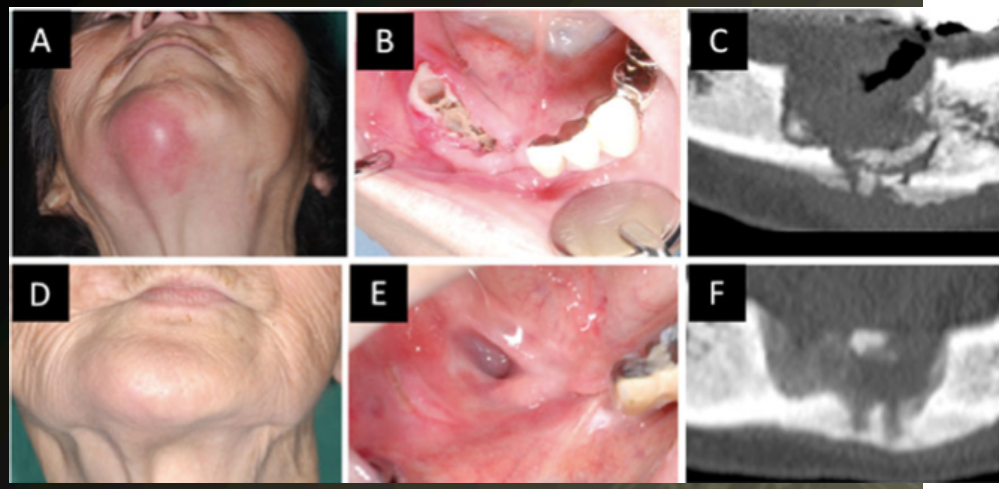
Teriparatide Hormone



Yoshiga D et al. "***Weekly teriparatide injections successfully treated advanced bisphosphonate-related osteonecrosis of the jaws***". Osteoporos Int (2013) 24:2365-2369





Teriparatide Hormone

Pelaz A et al. "***Alternative treatments for oral bisphosphonate-related osteonecrosis of the jaws: a pilot study comparing fibrin rich in growth factors and teriparatide***". Med Oral Patol Cir Bucal – Article in press – doi: 10.4317/medoral.19458

Stage III – BRONJ
9 patients

Group A

Plasma rich in growth factors

General anesthesia or Local anesthesia + conscious sedation

Bone sequestration and curettage of the subjacent bone

Plasma application and suture

Group B

Teriparatide administration

20 µg once daily by self-administered subcutaneous injection was at the baseline visit, and women attended monthly follow-up visits up to 6 months after discontinuing the teriparatide treatment. The maximum time of teriparatide administration was restricted to 10 months

Teriparatide Hormone

Pelaz A et al. "***Alternative treatments for oral bisphosphonate-related osteonecrosis of the jaws: a pilot study comparing fibrin rich in growth factors and teriparatide***". Med Oral Patol Cir Bucal – Article in press – doi: 10.4317/medoral.19458

- Osteonecrosis recovery was reached only with exclusive teriparatide treatment while in other ones it was necessary to combine bone anabolizant factor with antibiotics and surgery.
- The use of teriparatide as BRONJ treatment is still limited and that it has a low scientific evidence level.
- The use of teriparatide is contraindicated in patients with metastatic cancer because of its participation in the promotion of metastasis

Teriparatide Hormone

Alberto Bedogni Giuseppina Campisi Vittorio Fusco Alessandro Agrillo

Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione

La scelta di utilizzare teriparatide per il trattamento della BRONJ in pazienti non oncologici deve essere valutata caso per caso, l'eventuale indicazione deve essere condivisa con l'esperto in osteoporosi o lo specialista in Medicina Interna, e l'inizio della terapia è subordinata alla certificata consapevolezza da parte del paziente circa l'assenza di una indicazione ministeriale specifica al suo utilizzo per la BRONJ (acquisizione del consenso a terapia off-label).

Management strategies

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  - Ozone Therapy

Oxygen hyperbaric therapy

Freiberger JJ, Padilla-Burgos R, Chhoeu AH, Kraft KH, Boneta O, Moon RE, Piantadosi CA.: Hyperbaric oxygen treatment and bisphosphonate-induced osteonecrosis of the jaw: a case series. J Oral Maxillofac Surg. 2007 Jul;65(7):1321-7

Magopoulos C, Karakinaris G, Telioudis Z, Vahtsevanos K, Dimitrakopoulos I, Antoniadis K, Delaroudis S.: Osteonecrosis of the jaws due to bisphosphonate use. A review of 60 cases and treatment proposals. Am J Otolaryngol. 2007 May-Jun;28(3):158-63.

Yamazaki Y, Kitagawa Y, Hata H, Abe T, Murai C, Shiga T, Tamaki N.: Use of FDG PET to evaluate hyperbaric oxygen therapy for bisphosphonate-related osteonecrosis of the jaw. Clin Nucl Med. 2010 Aug;35(8):590-1

Oxygen hyperbaric therapy

What Is the Role of Hyperbaric Oxygen in the Management of Bisphosphonate-Related Osteonecrosis of the Jaw: A Randomized Controlled Trial of Hyperbaric Oxygen as an Adjunct to Surgery and Antibiotics

John J. Freiberger, MD, MPH, Rebecca Padilla-Burgos, RN,†*
Thomas McGraw, MD,‡ Hagir B. Suliman, PhD,§
Kevin H. Kraft, RN,‖ Bryant W. Stolp, MD,¶
*Richard E. Moon, MD,# and Claude A. Piantadosi, MD***

J Oral Maxillofac Surg 70:1573-1583, 2012

RECOMMENDATIONS

The authors' cumulative insights into the clinical management of ONJ lead them to recommend HBO as part of a multimodal therapy in severe cases where deep-seated soft tissue infection or refractory osteomyelitis is present. It will hasten healing, rapidly decrease pain and swelling, and help prevent further deterioration in QOL. This is foreseeable considering that HBO is known to decrease edema and inflammation, augment microbial killing,[51,52] and invoke stem cell mobilization,[53,54] vasculogenesis,[55] and tissue repair[18,56-62] in other wounds. Superficial and less complex ONJ lesions may heal spontaneously if they are properly debrided and infection is treated with appropriate antibiotics.

Oxygen hyperbaric therapy

Alberto Bedogni Giuseppina Campisi Vittorio Fusco Alessandro Agrillo

Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione

L'ossigenoterapia iperbarica deve essere intesa ad oggi come un trattamento sintomatico e quindi dovrebbe essere offerto ai pazienti, dopo attenta valutazione dei vantaggi e degli svantaggi legati ad una terapia alquanto impegnativa per il soggetto coinvolto, solo in associazione ad altri trattamenti che offrono maggiori garanzie di controllo della malattia (i.e. antibiotico-terapia e chirurgia).

Management strategies

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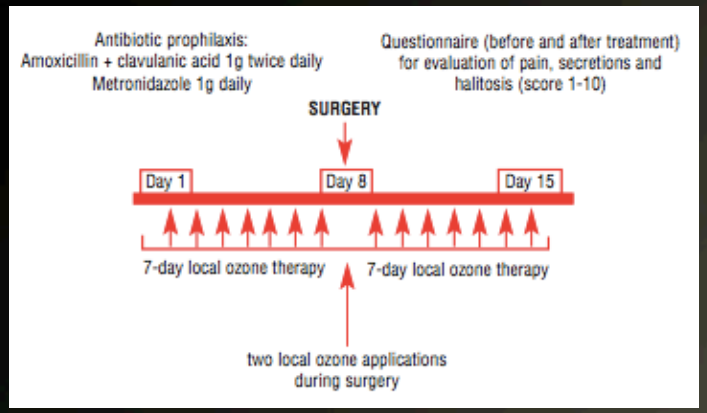
  - Ozone Therapy

Ozone Therapy

Petrucci MT, Agrillo A et al. "***Role of ozone therapy in the treatment of osteonecrosis of the jaws in multiple myeloma patients***". Haematologica 2007; 92: 1289-1290

12 patients affected by multiple myeloma with diagnosed ONJ

Protocol →



8 patients → Complete resolution of ONJ

4 patients → Improvement with persistence of the lesion

Oral Oncology
Head and Neck Oncology

Ozone Therapy

Ripamonti CI et al. "***Efficacy and safety of medical ozone (O3) delivered in oil suspension applications for the treatment of osteonecrosis of the jaw in patients with bone metastates treated with bisphosphonates: preliminary results of a phase I-II study***". Oral Oncology 47 (2011): 185-190

Protocol

- Pretreatment with antibiotic therapy for 10 days before starting the medical O_3 oil treatment
- A maximum of 10 applications of O_3 oil once every 3 days
- Each O_3 oil application lasted 10 min
- The treatment was stopped when patients showed intolerable adverse effects
- Patients who did not show a clinical response and whose wound showed exposed bone but clean edges were eligible for surgical resection of the necrotic bone, rotation of the mucosa lap, and surgical joining of the two edges.

"Medical O_3 delivered in an oil suspension should be considered a promising, effective, safe and simple therapeutic option for the treatment of small ONJ lesion."

Ozone Therapy

Alberto Bedogni Giuseppina Campisi Vittorio Fusco Alessandro Agrillo

Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione

In attesa di una sua validazione definitiva, l'ozonoterapia può essere utilizzata come trattamento di supporto in particolari situazioni cliniche (impossibilità al trattamento chirurgico o rifiuto dello stesso, in caso di incompleta/ assente guarigione dopo applicazione dei protocolli standard)

Management strategies

- Laser
- Other therapies:
  - Surgical Management of ONJ (Fluorescence guided bone resection, Platelet-Rich Plasma, Bone Marrow Stem Cell)
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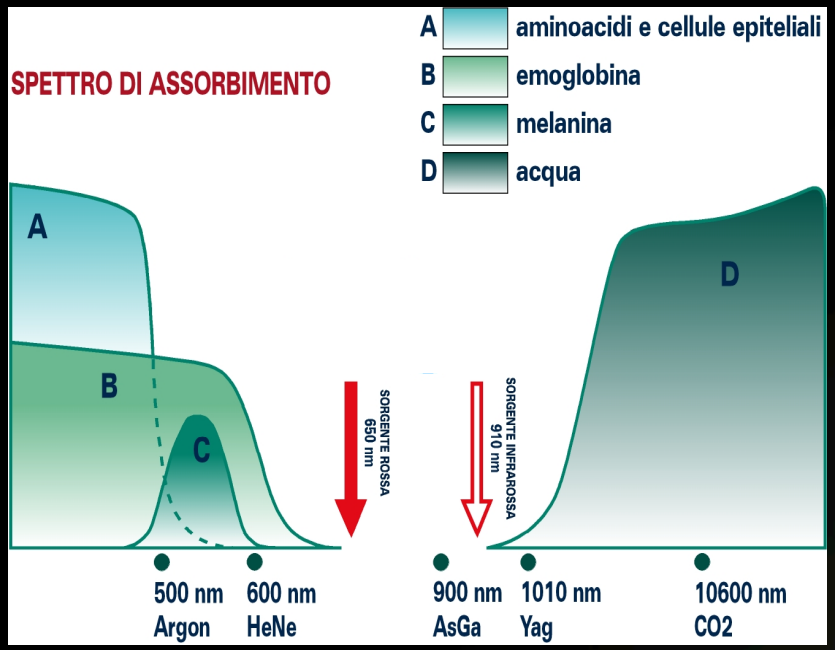
Laser

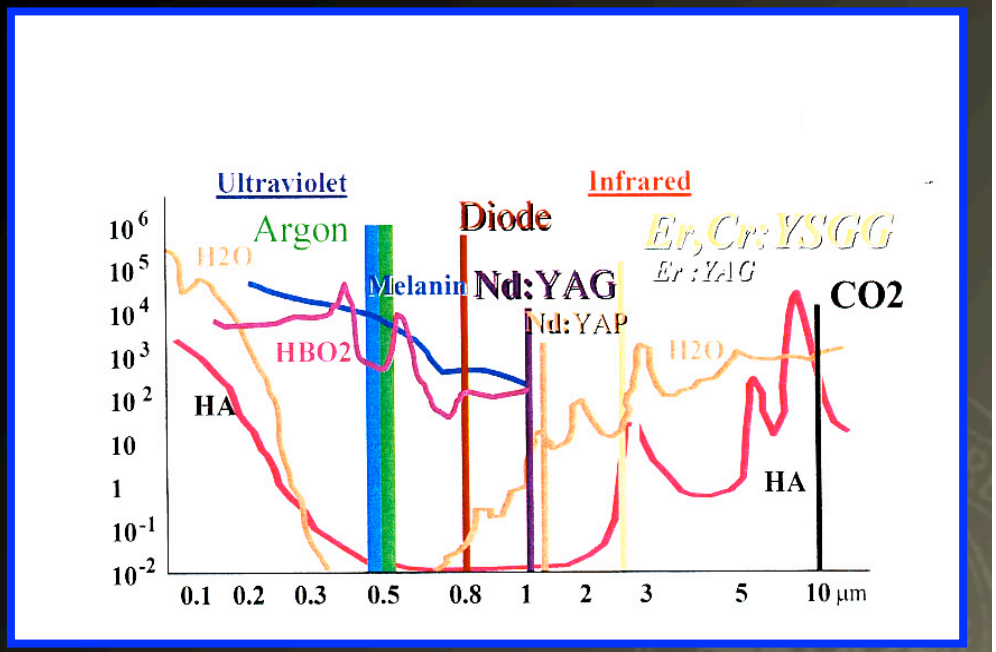
Low Level Laser Therapy - LLLT

"Soft laser"

Radiazioni a potenze minime

High Level Laser Therapy - HLLT

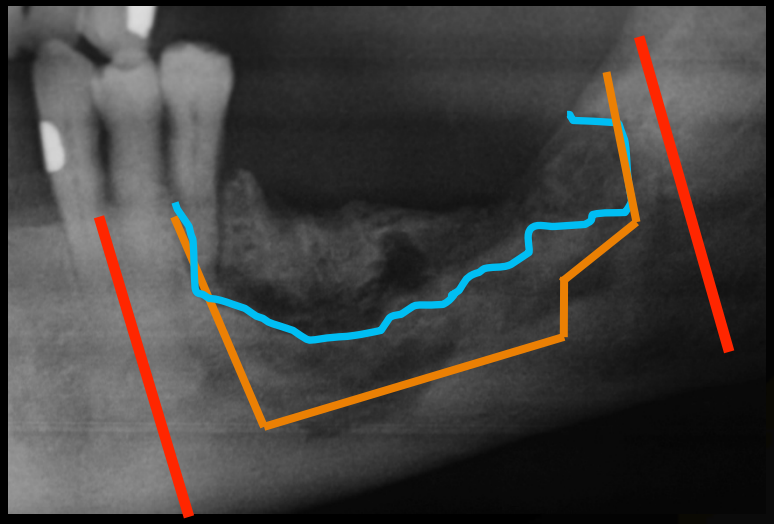


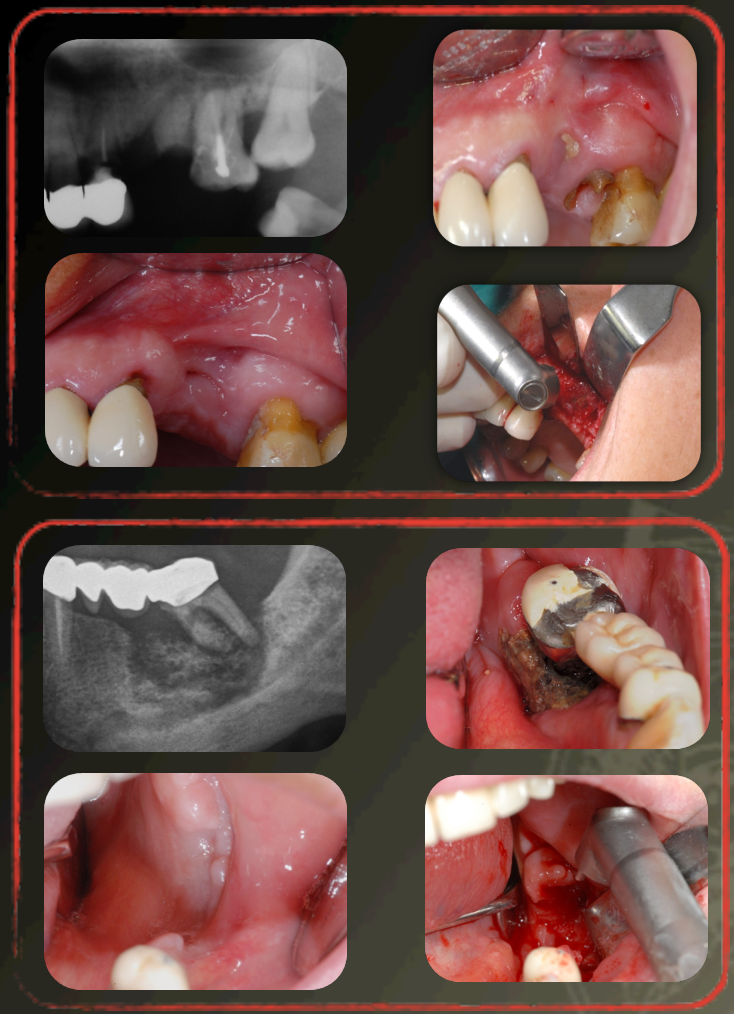


Lunghezza d'onda nella cosiddetta "finestra terapeutica", tra 600 e 1400nm

Laser Surgery
Er: YAG

Conservative treatment (antibiotic therapy, bone debridement) effective in about 50%-86% of BRONJ, with mucosal closure. More invasive surgical treatments (marginal resection, segmental resection) had success rate of 91,6%.





Laser Surgery

J Oral Maxillofac Surg. 2006 Sep;64(9):1460-2.

BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS (BON) OF THE JAWS: A POSSIBLE TREATMENT?

To the Editor:—Management of bisphosphonate-associated osteonecrosis (BON) of the jaws is currently a very topical subject. At present, there is no effective treatment for this condition. Several authors have recommended that prevention, when possible, of BON in patients at risk is the gold standard. In established cases, bisphosphonate therapy should not be discontinued; aggressive surgery of bone defects is mostly counterproductive, and furthermore, hyperbaric oxygen is of no benefit to patients affected with BON. In accordance with these restrictive therapy guidelines, the conclusion has been that these patients must and can live with some exposed bone in the oral cavity.[1-3]

Intermittent or continuous antibiotic therapy (penicillin V-K 500 mg, 4 times daily in association with metronidazole 500 mg, 3 times daily) has been shown to be beneficial as symptomatic treatment.[1,2] However, bisphosphonates are commonly prescribed (both intravenously and orally) for a range of conditions including osteoporosis, Paget's disease, multiple myeloma, hypercalcemia of malignancy, and bone metastases of malignancies (such as breast and prostate

As a consequence, we have begun to introduce Nd:YAG laser biostimulation (125 W, 15 Hz, 60 seconds for 5 applications, fiber 320 μm) as an additional tool in the treatment of BON lesions. Between 2004 and 2006 we examined 26 patients affected by this condition (9 patients affected by multiple myeloma, 14 treated for bone metastases of malignancies, and 3 for severe osteoporosis) who were subdivided into 4 different groups (as a result of developing therapy schemes). Six patients were treated with a surgical approach plus antibiotics, 6 with antibiotics only, 6 with laser biostimulation associated with antibiotics, and 8 with laser biostimulation applied after surgical debridement, removal of necrotic bone, and antibiotic therapy.

Of the 14 patients who underwent laser biostimulation, 9 reported complete clinical success (no pain, no symptoms of infections, and neither signs of exposed bone nor draining fistulas) with a follow-up of between 4 to 7 months (Figs 1-3). Two patients improved their symptomatology only. Three patients reported no clinical improvement.

Conversely, of the remaining 12 patients where the laser was not used, only 4 had a clinical success and 1 reported no pain, although the exposed bone was still visible in the oral cavity.

While these findings are not conclusive, they may be a step forward for improved management of this condition.

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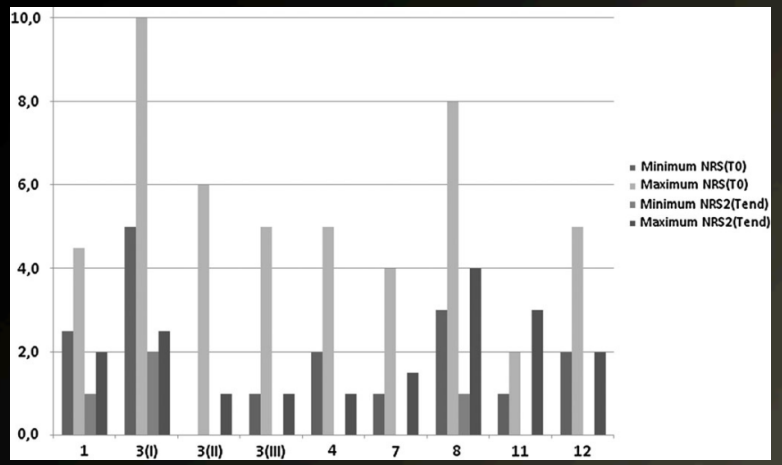
ELISABETTA MERIGO, DDS
MARCO MELETI, DDS
MADDALENA MANFREDI, DDS, PHD
Parma, Italy

Photomedicine and Laser Surgery

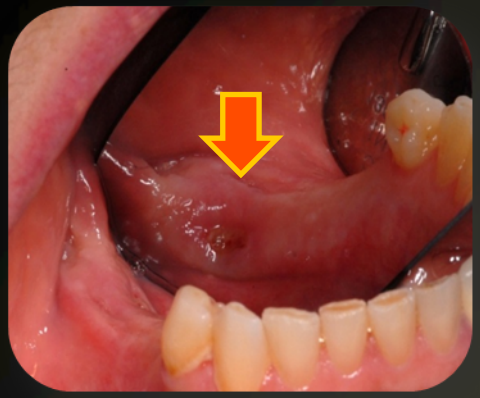
Laser Therapy

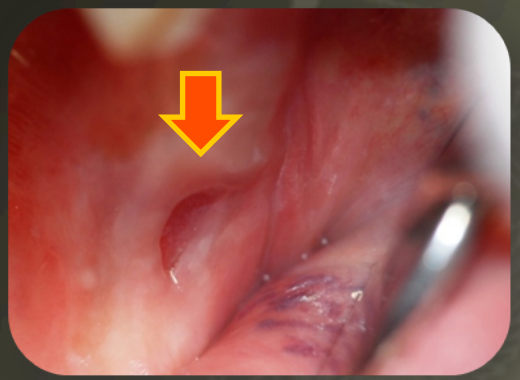
Romeo U et al."***Observation of pain control in patients with bisphosphonate-induced osteonecrosis using low level laser therapy: preliminary results***". Photomedicine and Laser Surgery Vol 29, N. 7, 2011: 447-452

Statistically significant difference ($p<0.05$) between the higher NRS scores before and after the protocol



General improvement of the clinical conditions, with spontaneous bone removal, full or partial mucosal closure.





Oral Oncology
Head and Neck Oncology

Laser Therapy

Martins MAT et al.“***Association of laser phototherapy with PRP improves healing of bisphosphonate-related osteonecrosis of the jaws in cancer patients: a preliminary study***”. Oral Oncology 48 (2012), 79-84

Stage I - Stage II - Stage III

Clinical Protocols: Pharmacological therapy, Surgical protocol, PRP plus LPT

“Most of the patients that presented a complete response, showing non-exposed bone, were treated with pharmacological therapy plus surgical therapy and PRP plus LPT.

The biomechanical effect of necrotic bone resection, the biologic effect of osteoinductive factors like PRP, and the biophysical properties of LPT proved successful in the management of BRONJ.

An improvement in angiogenesis, cell proliferation and extracellular matrix synthesis induced by LPT and PRP.”

MEDICINA ORAL
PATOLOGÍA ORAL
Y CIRUGÍA BUCAL
pISSN 1698-4447 eISSN: 1698-6946

Laser Therapy

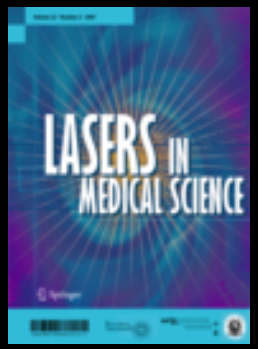
Vescovi P et al. "***Case series of 589 tooth extractions in patients under bisphosphonates therapy. Proposal of a clinical protocol supported by Nd: YAG low-level laser therapy***". Med Oral Patol Oral Cir Bucal 2013 Jul 1;18 (4):e680-5

"LLLT described here and the suggested prophylactic protocol, has been effective, for reducing the incidence of BRONJ after tooth extractions and limit the spread of odontogenic infections in patients already debilitated by systemic disease"

1	Systemic antibiotics (amoxicillin - 2 grams per day, 3 days before tooth extractions).
2	Intra-operative irrigations of the alveolar socket with povidone iodine solution + LLLT application (Nd:YAG laser: 1,25 W, 15 Hz – 1 minute for 5 times).
3	Systemic antibiotics (amoxicillin - 2 grams per day for 14 days until suture removal); mouthwashes with chlorhexidine and hydrogen peroxide (3 times per day).
4	LLLT weekly applications for the first 6 weeks and additional applications until complete mucosal healing.
5	Monthly follow-up visits for the first 2 months, and then every 3 and 6 months. OPT after 6 and 12 months.

LLLT = low level laser therapy.

Laser Therapy

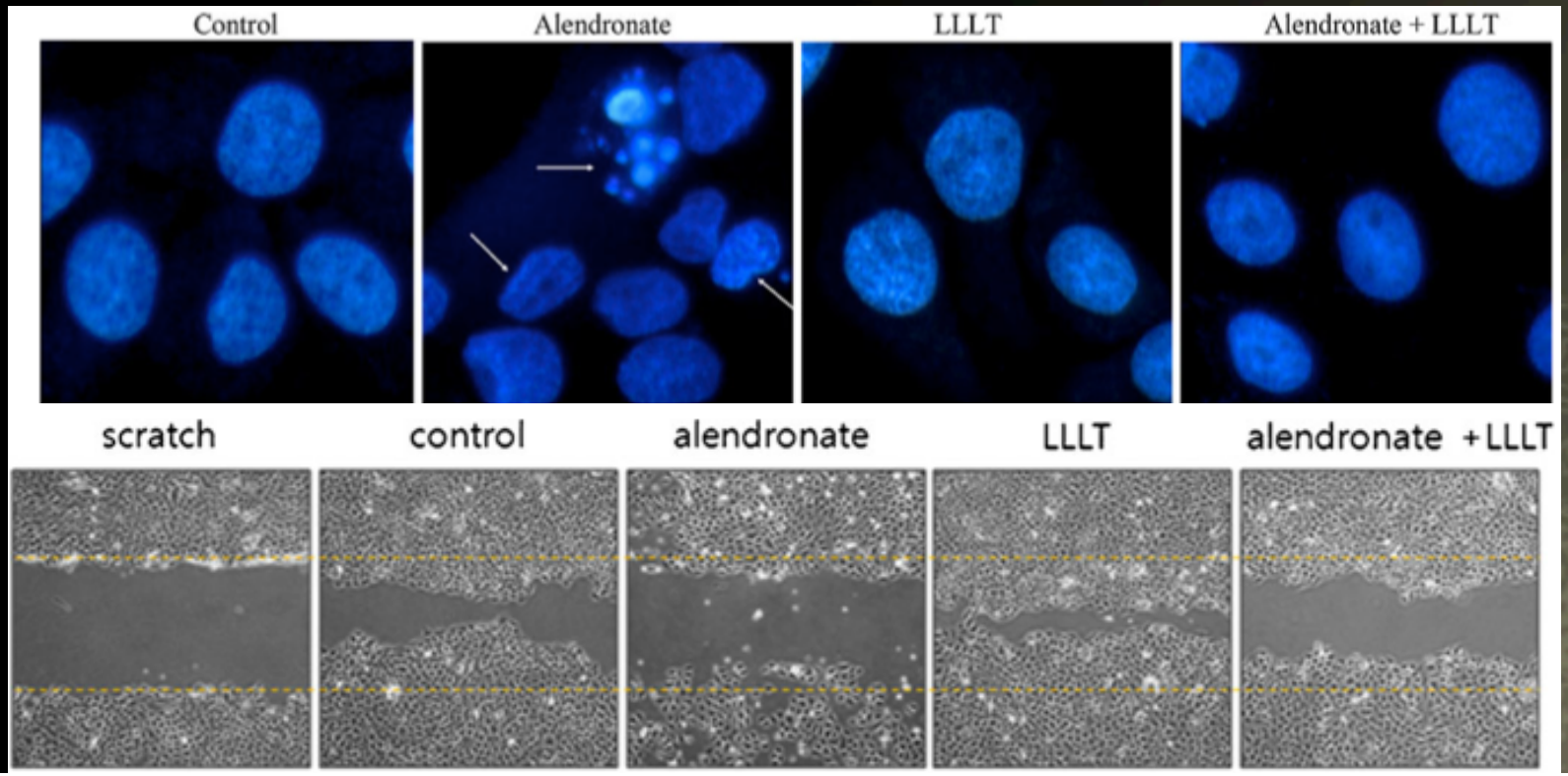


Lasers Med Sci
DOI 10.1007/s10103-013-1382-6

ORIGINAL ARTICLE

Effect of low-level laser therapy on oral keratinocytes exposed to bisphosphonate

Jae-Yeol Lee · In-Ryoung Kim · Bong-Soo Park · Yong-Deok Kim · In-Kyo Chung · Jae-Min Song · Sang-Hun Shin



Laser Therapy

Extractions Surgery + LLLT (Low Level Laser Therapy)

Appliable to all patients needing an extraction during intravenous BP therapy or long term oral BP therapy that cannot be suspended.
Lumix2®; FISIOLINE, Verduno, Cuneo, Italy) λ=650 nm (continuous mode, AO=100mW), 904-910 nm (super-pulsed mode 30KHz, average power 500mW, pulse duration 200ns). Biostimulation program
Round spot, diameter=8mm
T=900 sec 243J

Laser

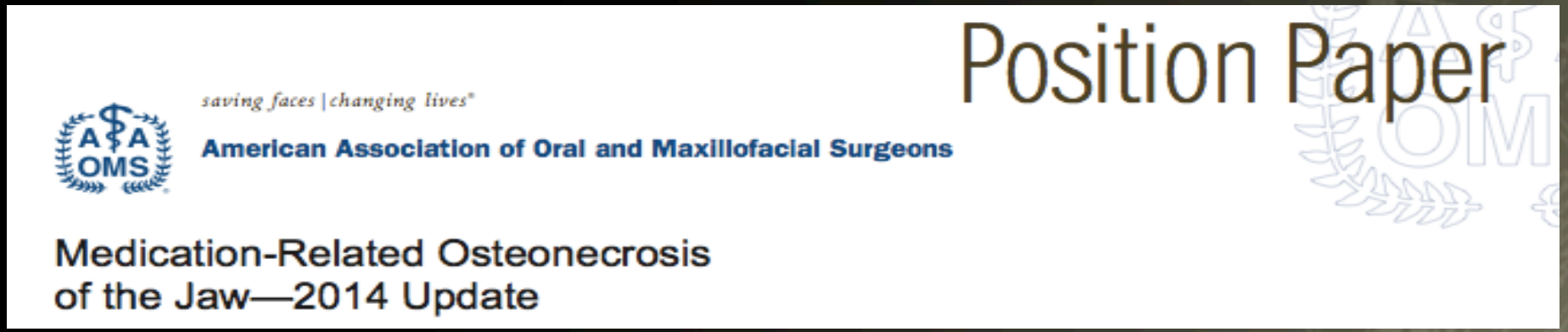
Alberto Bedogni Giuseppina Campisi Vittorio Fusco Alessandro Agrillo

Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione

In attesa di una sua validazione definitiva, la biostimolazione laser può essere utilizzata come trattamento di supporto in determinate situazioni cliniche (i.e. impossibilità al trattamento chirurgico o rifiuto dello stesso o per pochi o nessun risultato da protocolli standard)

CONCLUSIONS

The efficacy of these treatment modalities needs to be established through additional research and controlled studies.



Trattamento della ONJ: update della letteratura. Laser e altre terapie

Umberto Romeo

10 Maggio 2014, Alessandria

EUROPEAN MASTER DEGREE: ORAL LASER APPLICATIONS