

Surgery alone vs surgery plus PRP in the treatment of Medication-related Osteonecrosis of the Jaws. A clinical trial.



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FINAL PROJECT
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2014

*I would like to express my special thanks to my tutor, Manel Gorina,
for showing and teaching me the world of the maxillofacial surgery.*

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1.ABBREVIATIONS

- AAOMS: American Association of Oral and Maxillofacial Surgeons
- BPs: Bisphosphonates
- CT: Computed Tomography
- MRONJ: Medication-Related Osteonecrosis of the Jaws
- OPG: Orthopantomography
- PhE: Physical Examination
- PPGF: Plasma Poor in Growth Factors
- PRGF: Plasma Rich in Growth Factors
- PRP: Platelet-Rich Plasma
- SD: Standard Deviation
- VAS: Visual Analogue Scale

2.ABSTRACT

PURPOSE: To compare the incidence of dehiscence after a surgical approach plus PRP versus a surgical approach alone on those patients who suffered from MRONJ and who have clinical signs and symptoms with or without bone exposure. As secondary objectives we define to compare the number of reinterventions performed, the pain symptomatology and the quality of life before and after the treatment in patients treated with a surgical approach plus PRP versus patients treated with a surgical approach alone for the treatment of MRONJ in stage 0, II or III.

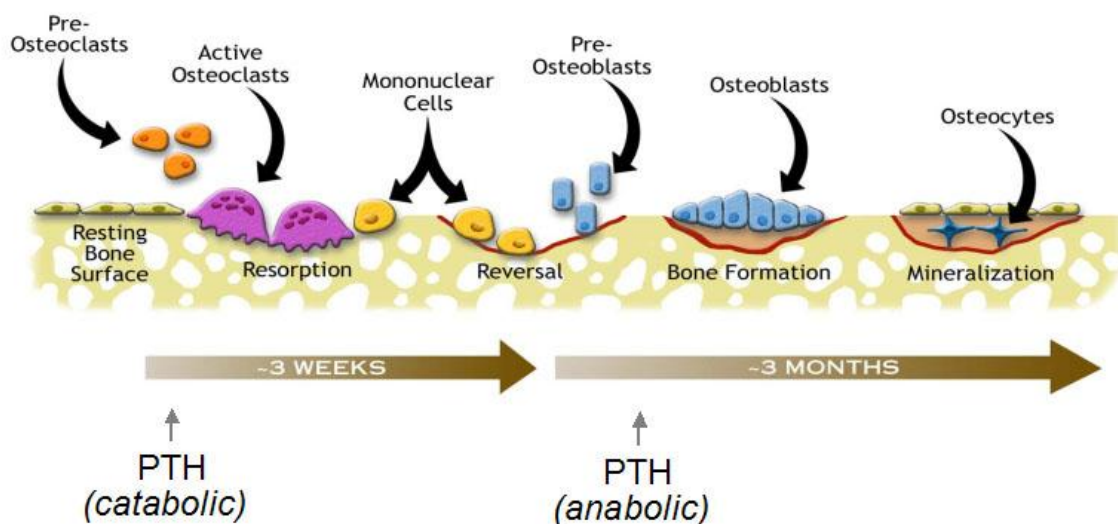
DESIGN: A three years long clinical trial, with simple-blind and randomize distribution of the sample, surgery alone or surgery plus PRP in the treatment of MRONJ.

3.INTRODUCTION

Medical related osteonecrosis of the jaws (MRONJ), also known as Bisphosphonate-Induced osteonecrosis of the jaws or ostechemonecrosis of the jaws, is a disease caused by the effect of bisphosphonates. In 2002 E. Marx (1) described for the first time that patients who were taking bisphosphonates developed non-healing bone exposure of the jaws with a similar clinical presentation as osteomyelitis which can even fistulate through the skin and provoke acute oral fetor(2). Curiously, there was a similar disease on the nineteenth century observed on phosphate miners which was called “Phossy jaw”(1,3). It has been observed a growing number of cases associated with other antiresorptive (denosumab) and antiangiogenic therapies. That’s the reason of the change of the pathology’s name (4).

Bisphosphonates (BPs) are drugs used to treat bone metastasis and other pathologies in which the problem is the elevated bone resorption like Paget Disease, Osteoporosis or hypercalcemia of the malignancy. These drugs inhibit bone resorption. They bound easily to the bone surface and when bone remodelling takes place osteoclasts ingest the bisphosphonate which blocks the formation of the enzyme that prevents osteoclasts apoptosis. So this osteoclast dies. And without it, new osteoid cannot be formed giving an elongated life to the old bone. But the osteocyte is not everlasting, so sooner or later dies too, leaving dead bone behind. The osteocyte function is to maintain and produce the bone matrix, so without the osteoclasts it only adds more layers of bone producing hypermineralization. The clinical consequence of this hypermineralization is the sclerosis of lamina dura and generalized osteosclerosis in the alveolar bone(1,5).

Bone Remodeling Cycle



It occurs only in the jaws. And it starts always in the alveolar bone. That's because the remodeling rate of this bone is higher than the rest of the bones' rate. In consequence, its uptake of bisphosphonate is also higher. This increased rate is explained by the forces generated when we chew. These forces create a tension in the lamina dura making necessary a regular remodeling process. However, if the accumulation of bisphosphonate in the alveolar bone is high, the lamina dura cannot remodels and becomes hypermineralized. If the remodeling demands continuous or a trauma such a tooth removal occurs while bisphosphonate accumulates, the alveolar bone cannot form new bone and it becomes necrotic. The blood supply that irrigates the overlying mucosa which comes from the underlying bone is disrupted and because of it the mucosa breaks down leaving exposed bone(1). That's the reason why tooth extractions, minor surgical interventions or any kind of dental manipulation during the bisphosphonate treatment have been identified as risk factors to develop MRONJ (3).

Most of our patients had been taking zoledronic acid (Zometa®), which is indicated for the treatment of tumor-induced hypercalcemia(6). Other bisphosphonates, like alendronic acid or pamidronate which are administered orally, are indicated for prevention of skeletal complications in some pathologies affecting bone as multiple myeloma, osteoporosis or Paget's disease. Zoledronic acid is a nitrogen-containing bisphosphonate and the most potent one. It is administered intravenously in a dose of 4mg over a period of 15 minutes once a month (5,7,8). It can induce exposed bone in 6-12 months, whereas the oral administered bisphosphonates like alendronic acid need at least 3 years to produce it because of its lower absorption(1). Because of that, a patient with bone exposure in the jaws with an intake of oral bisphosphonates during less than

2,5 years and patients with an intake of intravenous bisphosphonates during less than 3 months will not be included in the study.

MRONJ is described by the American Association of Oral and Maxillofacial Surgeons (AAOMS) as a *condition of exposed bone in the mandible or maxilla or bone that can be probed through an intraoral or extraoral fistula that persists for more than 8 weeks in a patient who has taken or currently is taking a bisphosphonate or other antiresorptive or antiangiogenic agent and who has no history of radiation therapy to the jaws.*

As a risk factors to develop MRONJ have been described any kind of dental manipulation or trauma during the treatment with BPs. This is the reason to formulate some preventive procedures which include, logically, avoiding any invasive dental surgery after the treatment with BPs has been initiated, to educate the patient to take care of his oral health and to treat any inflammation or pathology before start the BPs, also including the extraction of some teeth if they are incurable(1,3,9).

It is recommended, in all the patients in control with an oral and maxillofacial surgeon because of the uptake of BPs, to have a radiograph. It would be useful for the clinical control and to make an early diagnose observing the radiograph signs (figure 2) of MRONJ. These signs are:

- Osteolysis.
- Generalized increase of the density of the alveolar bone or,
- Widening of the periodontal ligament space.

Figure 2: radiographical signs



When a patient is diagnosed from MRONJ we recommend stopping the BP intake until the MRONJ is solved although it is not clear yet(10).

Depending on the clinical manifestations the AAOMS has classified the patients into different stages(1,4,11).

- **STAGE 0:** Non-exposed bone variant. Patients without clinical evidence of necrotic bone but present with unspecific symptoms or radiological findings that include:

SYMPTOMS	Odontalgia without an odontogenic cause.
	Dull aching bone pain in the mandible body.
	Sinus pain.
	Altered neurosensory function.
CLINICAL FINDINGS	Loosing of teeth without chronic periodontal disease.
	Periapical or periodontal fistula without relation with pulpal necrosis due to caries.
RADIOGRAPHIC FINDINGS	Alveolar bone loss or resorption not ascribable to chronic periodontal disease.
	Changes to trabecular pattern.
	Regions of osteosclerosis
	Thickening or obscuring of periodontal ligament.

- **STAGE I:** patients with exposed bone or fistulae that probes to bone but without pain or any symptomatology.
 - Ia: the largest area of exposed bone is less than 1cm.
 - Ib: the largest area of exposed bone is more than 1cm.
- **STAGE II:** patients with exposed bone or fistulae that probe the bone accompanied by pain and other symptomatology.

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- IIa: the largest area of exposed bone is less than 2cm.
- IIb: the largest area of exposed bone is more than 2cm.
- **STAGE III:** patients with exposed bone or fistulae that probe the bone and one or more of the following:
 - Exposed necrotic bone extending beyond the alveolar bone.
 - Pathologic fracture.
 - Extraoral fistula.
 - Oral antral or oral nasal communication.
 - Osteolysis extending to the inferior border of the mandible or sinus floor.

Figure3: MRONJ stage III



The most common situation of the bone exposure is in the molar area and about the 69% of the patients is classified, at least, as a stage II.

The treatment will depend on the clinical stage(1,12):

- **STAGE 0** (non-exposed variant): Systemic management and conservative measures like antibiotic (0.12% chlorhexidine oral rinses three times daily + penicillin VK 500mg four times daily) and if the conservative management fails, surgical debridement or resection.
- **STAGE Ia and Ib:** these patients have no symptoms so they don't need to be treated.
- **STAGE II:** in these stages there are infection and pain so they will need antibiotic (0.12% chlorhexidine oral rinses three times daily + penicillin VK

500mg four times daily) and if the conservative management fails, surgical debridement or resection.

- STAGE III: these patients must be treated with the same antibiotic measures adding bone resection directly.

Figure 4: MRONJ stage IIa



Figure 5: MRONJ stage II after the surgery



STAGE	DEFINITION	TREATMENT
STAGE 0	Non-exposed bone variant with clinical signs and symptoms, including pain, and radiographic findings.	1. Conservative management. 2. When it fails, surgical bone resection.
STAGE I	Exposed bone without symptoms.	Hygienic measures.
STAGE II	Exposed bone with pain and other symptoms.	1. Conservative management. 2. When it fails, surgical bone resection.
STAGE III	Exposed bone plus exposed bone extending beyond the alveolar bone region, pathologic fracture, extraoral fistula, oral antral/oral nasal communication or/and osteolysis extending to the inferior border of the mandible or sinus floor.	Surgical resection plus antibiotic measures.

Stages 0 and II are recommended to be treated first with a conservative approach. But it has been shown that without surgery the MRONJ cannot be healed, that only reduces the pain and, at the end, after some weeks or months, the patient I considered resistant to conservative management and is operated. It has been seen that respective surgery is better than local debridement (13).

In case the bone resection is needed, it is difficult to know where the symptomatic bone ends to know how much bone we have to remove (11). A study suggests the use of tetracycline-induced bone fluorescence to know where the necrotic bone finishes because tetracycline induces fluorescence only in healthy bone (14). Treatment with hyperbaric oxygen as an adjuvant therapy to the surgery does not show statistically significant difference in clinical outcome (15). With this surgical treatment protocol by Marx only the few patients they treat with resection of bone were totally recovered. The remainder of the patients was free of symptoms but they had still exposed bone which can be reinfected. At our hospital, we have observed that our patients must be operated more than one time, with a ratio of more or less 1.3 surgical interventions per patient. It is due to the incidence of dehiscence per patient after the surgery.

Now, there are some studies that are investigating the results of treating the patients with bone resection combined with the use of platelet-rich plasma (PRP)(16). The efficacy of some cellular mediators as angiogenic growth factors, bone morphogenetic proteins or interleukins has been shown in the clinical practice. Platelet-rich plasma is an autologous source of protein growth factors obtained by density centrifugation. Through this process, explained in detail in the intervention section, we obtain a very high concentration of human platelets and protein growth factors secreted by platelets

which initiate wound healing (17). There are some studies of series of cases that described a combined treatment with bone resection and PRP with success rates about 80-100% (17,18).

4.JUSTIFICATION

MRONJ is a disabling disease for the patients who suffer it. It affects their life quality by producing pain, infection, creating fistulas, provoking oral fetor, causing difficulties to eat because of all these symptoms and the tooth loss. Due to all these signs and symptoms the social and working life of the patient can be affected. We must be aware that most of our patients are suffering from a malignant metastatic disease. This fact decreases their life expectancy making their life quality even more important.

An exposed bone is always a direct portal of entry of bacteria. In our patients, remembering that most are cancer patients who have been treated with chemotherapy which decreases their immunologic system, the risk of infection is considerably higher than in the rest of the population. Hence here lies the importance of closing this gate eliminating the actual infection and preventing future infection. If the treatment is effective and there is no dehiscence of the wound which implies new bone exposure, the risk of infection will diminish. And all this will drive our patients to an improvement in their life quality.

We are proposing to use PRP as an adjuvant therapy to the surgery. As it is explained in the introduction it has been shown that the conservative management with antibiotics and chlorhexidine doesn't work. Due to the multifactorial etiology, not entirely clear yet, it would be interesting to study combined treatments. Since PRP is a source of growth

factors involved in wound healing it could be an adequate treatment for this pathology combined, of course, with necrotic and infected bone resection and antibiotic treatment. To this we should add the economic impact that all this process involves. The actual treatment, the surgery followed by seven days of antibiotic but without PRP, has a dehiscence ratio of 1.3 approx. It means that a lot of patients have been reoperated. If we can reduce the number of dehiscence, we will also reduce the number of reinterventions, decreasing also the patients' inconvenience that it carries. This is reflected in a decreased cost for the health system.

5.HYPOTHESIS

So, knowing the PRP characteristics our hypothesis is that patients treated with surgery plus PRP will have less dehiscences than patients treated with surgery alone, and it will incur a lower number of interventions per patient.

6.OBJECTIVES

6.1. MAIN OBJECTIVE

In this study we want to compare the incidence of dehiscence after a surgical approach plus PRP versus a surgical approach alone on those patients who suffered from MRONJ and who have clinical signs and symptoms with or without bone exposure (it means in patients whose MRONJ stage is 0, II or III).

6.2. SECONDARY OBJECTIVES

- Compare the number of reinterventions performed in patients treated with a surgical approach plus PRP versus patients treated with a surgical approach alone in patients with MRONJ in stage 0, II or III.
- Compare the pain symptomatology before and after the surgery in patients with MRONJ in stage 0, II or III.
- Measure the quality of life of patients with MRONJ in stage 0, II or III before and after the surgery to know how the pathology affects their lives.

7.METHODS

7.1. STUDY DESIGN

The best way to confirm or refuse our hypothesis with a high level of evidence is doing a clinical trial. This clinical trial will be controlled, randomized, simple blind and unicentric. It will take place in the Universitary Hospital of Girona Dr Josep Trueta and its duration will be of 3 years.

7.2. POPULATION OF INTEREST

To know which patients are going to participate in this clinical trial we have to define our population of interest. This group will be composed by those patients who are suffering from MRONJ stage 0, II or III, it means patients with clinical symptoms with or without bone exposure.

As inclusion criteria we define:

- Patients (men and women) diagnosed of MRONJ stage 0, II or III (the stages with indication of surgical treatment).
- Patients treated with oral bisphosphonates during at least 2 years or intravenous bisphosphonates during at least 1 months.
- Patients visited in the Universitary Hospital of Girona Dr. Josep Trueta.
- Participants must be 18 years or older.

As exclusion criteria:

- Patients who received radiation therapy to the jaws after being diagnosed from MRONJ.
- Patients with obvious or known metastatic disease to the jaws.
- Pregnancy.

7.3. SAMPLING

The sampling system will be consecutive so it won't be probabilistic. Every patient seeing in our department or referred to us and which meet criteria of inclusion and not exclusion will be enrolled in this clinical trial.

7.3.1. Sample size

As seen in most of the studies previously appointed and based on the clinical experience of oral and maxillofacial surgeons of the Universitary Hospital of Girona Dr Josep Trueta we estimate the incidence of dehiscences in patients treated with a surgical approach plus PRP will be 0.1 versus 0.6 in patients treated with a surgical approach alone. Therefore, assuming an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, we need 28 patients in each group to perceive a minimum relative risk of 0.16 if the tax of the non-exposed group is 0.6. We have estimated that the tax of follow up loses will be 40%, taking into account those patients that will not come to the follow up visits and those patients who will die because of their underlying disease. Acknowledging the incidence of MRONJ in the Universitary Hospital Of Girona Dr Josep Trueta which is around 30 cases per year we will need at least 2 years to reach the sample size to confirm or refuse our hypothesis with a high level of evidence.

7.4. RANDOMIZATION

Once the patient has been included in the study we will proceed to assigned him or her to one of the groups randomly avoiding, this way, the selection bias. As our sample system is consecutive, we have to use a randomization system which doesn't need to know the entire sample before randomizing it. Because of that we will use a covariate adaptive randomization where a new patient is sequentially assigned to a particular treatment group by taking into account the specific covariates and previous assignments

of participants. Using this randomization method we can control the influence of covariates in the result.

Covariates taking into consideration will be the way of BP's administration (orally or intravenously), the underlying disease and the concomitant administration of corticoids. Randomization plan will be generated by an external researcher using online software. It will be a SPSS program. This external researcher will be the one who will assign the patient to one of the groups, so the main researcher will not have access to the randomization sequence. So he will know which intervention he has to execute once the patient is in the operation room by receiving a closed envelope the same day of the intervention.

7.5. MASKING TECHNIQUES

Masking will be performed by blinding the patient, and so, turning the study into a simple blinded one. We will explain to the patient both treatment options using the information sheet (annex 1) and the informed consent (annex 2) as well as a short intervention debriefing. To blind the patient we will use the sham procedure which consists mainly of simulating the PRP intervention in the group that will not receive it. So, as the only difference the patient could be aware of is the extraction of blood to make the autologous PRP, we will extract blood from all the patients. The blood of those who will not receive PRP will be properly eliminated.

The main researcher cannot be blinded inasmuch as he is the one who will perform the surgery.

The statistical analysis of the data recorded will be done by an external statistician who will not know which treatment has received each patient, so he/she will be masked too.

7.6. PROCEDURES

7.6.1. Interventions

As it is explained above we will have two groups of similar patients. The first group will be treated with a surgical approach and the second group with the same surgical approach plus the application of PRP.

Every patient seeing in our department or referred to us and which meet criteria of inclusion and not exclusion will be enrolled in this clinical trial. Obviously, first of all patients must accept to enter in the study, so every candidate will be asked for the authorization to participate in the study by means of informed consent.

- **1st visit:**

All the patients will come to our consulting room, we will explore and diagnose clinically them and we will see if they are suitable or not to be included in the study. Clinical signs will consist of pain, swelling, halitosis, fistulas with or without exposed bone. As the AAOMS defines patients will be currently or previously in treatment with antiresorptive agents, in this case with bisphosphonates, with an evidence of exposed bone or the signs and symptoms named before for more than eight weeks and without history of radiation therapy or clear metastatic disease to the jaws. Each patient will be classified into the different stages described by the AAOMS on the 2014 update(4). In this first visit we will measure the pain using the VAS scale and the quality of life using the SF36 scale before the treatment, and we will collect the baseline data and variables (age, gender, BP medication, BP administration and dose, time of BP exposure, underlying disease, oral hygiene and administration of corticosteroids). Orthopantomograph (OPG) and computed tomography (CT) will be performed before and after the treatment. So we will have the images available the intervention's day.

All of them will receive antibiotic prophylaxis and hygienic advices. If there is not any allergy brought on by medication we will prescribe amoxicillin 2g to be taken orally one hour before the surgery. If the patient have allergy to penicillin we will prescribe clindamycin 600mg with the same posology. We will recommend between 6-8 hours of fasting before the intervention. We will advise the patient to come with someone, not alone. The patient will be asked to take off any intraoral material such as piercings or removal dental prosthesis.

- **2nd visit: Intervention day**
 - **BOTH GROUPS:**

Patients will be admitted to the hospital in an ambulatory major surgery regime.

In the morning of the same day the surgeon will receive an encrypted email with the group assignment of the patient.

Before injecting regional anesthesia a nurse will extract 1 tube of blood from all patients. In patients who will receive PRP the extraction will be done using the PRP kit (figure 6), and with the rest of patients, blood will be extracted using the habitual syringe since the purpose of the extraction is only to mask the patient. In case the patient will receive PRP, at this moment the nurse will be preparing it, as explained further.

If the affected area embraces the mandible we will induce block anesthesia of the inferior alveolar nerve (Vc) inoculating 40-80mg of articaine hydrochloride/0.005-0.01mg of adrenaline. Then we will anaesthetize the oral mucosa by infiltration around the future surgical area with 40-80mg articaine hydrochloride/0.005-0.01mg adrenaline. Dosage will depend on the extension of the affected area that we have to treat so we can

increase the dose directly proportional to the lesion size. After 5 minutes approx. we will start the surgery intervention.

First of all we will make an incision with scalpel #15 along the necrotic zone (if there is partial gum covering it) and widening the cut until 1cm until healthy gum appears. After that we will make discharge incisions to design the flap. Then we will open the mucoperiosteal flap and turn it over (like a fully opened book) exposing the necrotic area and making sure we can also see healthy bone tissue.

After that we remove the necrotic bone using a rongeur for bone and if remaining sharp edges or it has been impossible to remove all the avascular bone we will make a curettage using tungsten burs of different sizes (depending on the treatment area) with continuous stream of irrigation with physiologic serum to prevent overheating the healthy bone or other noble structures surrounding. This step will end when we see that the underlying bone has a physiologic dotted bleeding.

Adjacent teeth will be extracted if these are in direct contact with necrotic bone.

Resected bone will be sent to microbiological and anatomopathological analysis to know which antibiotic is the most indicated and to rule out bone metastasis in the zone.

- GROUP WITHOUT PRP:

At this point, in the first group of patients, we will closure the wound without tension through incisions made through the periosteum until the gum will be closed by a passive way. We will suture by first intention using dissolvable strings (Vycril® 4/0) which last 1 month approx.

- GROUP WITH PRP:

In the second group, before the closure, we will apply the PRP gel. So first we will obtain the PRP from the patient's blood.

At the beginning of the surgery, meanwhile the surgeon is injecting anesthesia and we wait to it to do its effect, the nurse will be preparing the PRP.

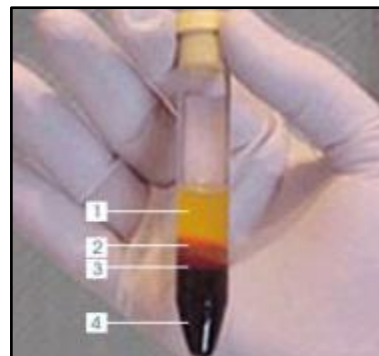
PRP preparation technique:

A nurse will draw twenty milliliters of blood from a peripheral vein of the patient using tubes of 20cc containing 3.8% trisodium citrate solution as an anticoagulant. Once all the tubes are filled they will be centrifuged at 3000rpm for 8 minutes at room temperature. With this process the blood will be separated into four components (figure 7): red blood cells at the bottom of the tube, just above them will be white blood cells, immediately above the plasma rich in growth factors (PRGF) and at the top of the tube the plasma poor in growth factors (PPGF). The PRGF (3cc per tube) and the PPGF will be collected and transferred to sterile tubes, separately. Calcium chloride (50µl) at 10% will be added for 1ml fraction of PPGF to activate it and make a gel, coagulating it. After 15 to 20 minutes a PPGF gel will be formatted. Once it is ready we will wait at least 10 minutes more before injecting it on the patient.

Figure 6: PRP kit



Figure 7: PRP tube (1.PPGF; 2.PRGF; 3.Leukocytes; 4. Red cells).



Before closing the wound we will inject the PRFG around the wound using a 30G needle and we will cover the bone surface with the PPGF gel to promote healing and to create a double sealed layer that protects from microbial infection. After that we will close the wound as explained for the group treated without PRP.

▪ **DISCHARGE INSTRUCTIONS FOR BOTH GROUPS:**

The patient will be told to follow a 7 day oral antibiotic treatment with amoxicillin 1g/8h if there are no allergies, or clindamycin 300mg/6h or levofloxacin 500mg/12h if there are allergies to penicillin.

We will recommend oral analgesia and anti-inflammatory treatment with ibuprofen 600mg/8h combined with paracetamol 1g/8h depending on the patient's needs. We will also prescribe gastric protection (omeprazole 20mg).

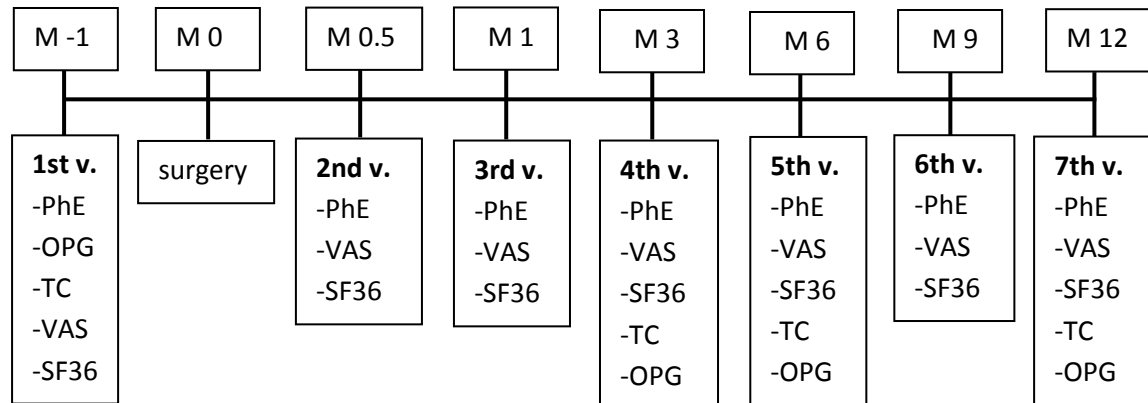
During the next 24 hours the patient cannot eat hot food or beverage. It is good to reduce and prevent the inflammation to apply ice in the zone. We also recommend eating soft foods and cold drinks during the next 7 days.

We will tell the patient to rinse the mouth with chlorhexidine diluted 1:1 with water during 15 days.

• **Control visits**

The patient will be followed up during one year with visits: 2 weeks, first, third, sixth, ninth and twelfth month after the surgery. In this visits we will ask the patient to go through the pain and quality of life questionnaires. We will also do a orthopantomograph (OPG) ant CT scan on the 3rd, 6th and 12th months. Our main variable will be evaluated in each visit exploring the patient and looking if the wound is completely closed with all the bone epithelized (no dehiscence) or if there is some exposed bone again (dehiscence).

7.6.2. Data collection scheme



7.7. VARIABLES

Every measure or data will be collected at the Universitary Hospital of Girona Dr Josep Trueta, where the patients will be visited and treated.

7.7.1 Main variable

The main variable of the study will be the incidence of dehiscences that occur during 1 year of clinical follow up with each intervention. A dehiscence will be defined as the bone exposure in the same site of the surgery incision. It will provoke a reinfection of the site and a recurrence of the MRONJ. If there is no dehiscence we will define our treatment as a success and we can consider that the patient is cured. We will collect this information in an anonymised table as “patient with dehiscence” and “patient without dehiscence” during every control visit. So it will be considered a qualitative variable. We will consider that there is a dehiscence when the bone has not been epithelialized or when, after being epithelialized, it is exposed again.

7.7.2. Independent variables

My independent variables are the two interventions explained above. They are qualitative variables.

7.7.3. Covariates

Demographic data such as age, gender and socioeconomic status will be recorded as covariates as well as the type of BP received, its administration way (intravenously or orally) and the time of exposure to it. Concomitant administration of corticoids will also be recorded as a potential confusion factor. With the underlying disease we will do the same procedure.

The oral hygiene will be also recorded as good hygiene and bad hygiene. It will be defined as bad hygiene when the patient doesn't go to his odontology controls and doesn't accomplish the recommended oral treatments. Alcohol consumption and smoking habit actual and previous to the occurrence of MRONJ will also be recorded.

7.7.4. Secondary variables

- Number of reinterventions will be collected as a secondary variable to know the correlation between them and the deshistences.
- Pain will be defined as a secondary variable. Using the VAS scale (annex 3) we will measure the pain in an objective way in every reexamination visit. This is self-administered. This scale represents pain in a line of 10cm, so the scale goes from 0 (no pain) to 10 (worst possible pain). It has above the line some pictures representing in a visual way the pain, in which a happy face represents no pain and a crying face represents worst pain. Depending on the results the patient will be classified into:
 - No pain: VAS 0
 - Low/moderate pain: VAS 1-3
 - Moderate/severe pain: VAS 4-6
 - Very intense pain: VAS >6

- Another secondary variable will be life quality. It will be measured using the SF-36 questionnaire (annex 4). This questionnaire consists of eight scaled scores, which include vitality, physical function, body pain, general health perceptions, physical role function, emotional role function, social role function and mental health. Each scale is transformed into a 0-100 scale assuming that each question carries equal weight. The lower score the more disability.

7.8. STATISTICAL ANALYSIS

The sample size calculation has been described in the section of sampling (6.3.1).

We will use the SPSS software to do the statistical analysis.

The univariate analysis of the qualitative variables will be done using proportions while the univariate analysis of the quantitative variables will be performed using the mean \pm SD if we can assume a normal distribution and if not, using the median.

In the bivariate analysis, the efficacy analysis will be done using relative risk estimation. To prove statistical association between the interventions and the presence of dehiscence a χ^2 test will be applied.

A multivariate analysis will be done to see the contribution of the covariates or possible confusion variables in the results. It will be made using a logistic regression model.

Lost data will be handled using the technique of last observation carried forward.

8. WORK PLAN

Researchers: Alba Torrillas (AT) and Manel Gorina (MG)

Collaborators: Monitor (MO), statistician (ST), nursing staff (NS).

The trial has been designed in 6 phases:

- **PHASE 0: PREPARATION PHASE** (2 months)

Researchers: AT and MG. From October 2014 to November 2014 the protocol will be written and presented to the Ethics Committee of Clinical Research.

- **PHASE I: COORDINATION PHASE** (1 month)

In December 2014 all investigators, collaborators and nursing staff will meet to coordinate the beginning of the trial. All the team will be informed about the work plan and schedule and the methods of data collection.

- **PHASE II: FIELD RESEARCH** (36 months)

- **PICK PATIENTS** (24 months): Researchers: AT, MG, ST and MO.

From January 2015 to January 2017 we will include in the study every patient that come to our office and that meet inclusion and no exclusion criteria. Patients will be randomly assigned to one of the intervention groups.

- **INTERVENTION** (24 months): Researchers: MG will perform the

surgery. NS will be as instrumentalist and will prepare the PRP. Every patient included will be operated using one of the two interventions depending on the group assigned randomly. If a patient has a dehiscence during the follow up period he/she will be operated again, so it can occur after the 24 months.

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- **FOLLOW UP** (36 months): Researcher: MG. Every patient will be followed up during 1 year through control visits every 3 months.

- **PHASE III: DATA COLLECTION** (36 months)

All investigators. Simultaneously with the trial development, data will be registered in the database. An analysis of data will be performed regularly by an external collaborator to control its evolution and verify that the protocol is being followed.

- **PHASE IV: DATA ANALYSIS** (1 month)

ST. After processing the database, all data will be analyzed using the appropriate statistical test by a statistician.

- **PHASE V: RESULTS INTERPRETATION** (1 month)

Investigators: MG and AT. An interpretation of the results will be performed and the corresponding articles will be written.

- **PHASE VI: PUBLICATION** (1 month)

Researchers: AT and MG. Write and edit the articles to publish them.

2014

9.CHRONOGRAM

	2014		2015	2016	2017	2018		
	Oct- Nov	Dec.	Jan-Dec	Jan-Dec	Jan-Dec	Jan	Feb	Mar
Preparation Phase								
Coordination Phase								
Pick patients								
Intervention								
Follow up								
Data collection								
Data analysis								
Interpretation results								
Publication								

10.ETHICAL AND LEGAL ASPECTS

As regulated by the law 14/2007 of the 3rd of July about biomedical investigation the project will be evaluated by the ethics committee of clinical research of the University Hospital of Girona Dr Josep Trueta. All participants will be informed about the interventions and the details of this clinical trial. They will be given an information sheet (annex 1) and they must sign the informed consent (annex 2) to participate in the study. Patients at all times have the right to leave the study with no impact on the health care they receive. Likewise, and in accordance with provisions of the organic law 15/1999 of the 13th of December about data protection, confidentiality and protection of personal data shall be guaranteed. All patients will be insured for the damage and prejudice that might result from the investigation. The principles of human experimentation are equally respected as provided by the Helsinki agreement.

An ethical dilemma that can arise is what to do with the blood extracted from those patients that will not receive PRP. As the extraction of blood is not a high risk intervention and the blood is obtained only to mask the patient, according with the provisions of the previous law the blood samples will be properly eliminated. It will be consulted with the ethics committee of clinical research.

11.LIMITATIONS

As the intervention and the follow up will be performed by the same surgeon a procedure bias could occur.

During the study implementation loses or withdrawals to follow up bias could also occur, and we will try to minimize it in the statistical analysis. The method used to handle the follow up loses, last observation carried forward, can overestimate the results, but taking into account the pathogenesis of the MRONJ, if the bone is totally covered by gum probably it is healthy bone.

One limitation is how to know when necrotic bone ends and healthy bone appears at the surgery. Although we describe that healthy bone appears when we see physiologic dotted bleeding, it is not an enough objective criteria and it is possible that some necrotic bone remains. The solution described by some authors (14,19) is to implement fluorescence-guided bone resection, but that's not implemented in our hospital yet.

Secondary variables are exploratory so they must be evaluated in a study *ad hoc*.

12.FEASIBILITY

In order to put this project into action we will form a suitable medical team and a multiprofessional team. The main investigator will be the surgeon who has considerable experience in the surgical treatment of MRONJ and in the use of PRP for other indications. The nurse who will be involved will be the habitual nurse who is used to this surgery and has been working with the surgeon during some years. She will be trained in the PRP preparation techniques.

As we do not have specialized professionals in statistics we will hire an external statistician to do the statistical analysis.

As the intervention without PRP is the usual surgery performed at the University Hospital of Girona Dr Josep Trueta, we have the operation room available two days per week, with all the instruments except the PRP kit and the centrifuge. The nurse assistant, the nurse and the surgeon are hired by the National Health System as well.

At our hospital we have around 30 patients per year diagnosed of MRONJ, so in the 3 years that we have established to include patients we can get the sample size.

13.BUDGET

In the feasibility section we have described the means available. And as we have said, we will hire a statistician to do the statistical analysis and to create the randomization sequence and then send to the nurse the envelopes with the intervention for each patient, remaining the sequence hidden. In order to comply with the legislation we will hire a monitor with professional training in monitoring clinical trials. He will monitor the data to control its quality and will write periodic reports and security reports to Agencia Española del Medicamento (Spanish Drug Agency) and all other institutions required.

The surgery is included in the National Health Service provisions, so we only have to buy the material needed to the PRP application, which include a centrifuge, the PRP kit (a closed-loop system) and extra tubes.

STAFF			
Monitor	2h/week x 36 months	20€/hour	5,760€
Statistician	40h + 1h/week x 24 months	35€/hour	4,760€
SUBTOTAL:			10,520€
MATERIAL			
Kit PRP	1 per patient x 28 patients	77.55x28=	2,171.40€
Tubes	1 per patient x 28 patients	29.98x28=	839.44€
Centrifuge			467.79€
Prints			10€
SUBTOTAL:			3,488.63€
PUBLICATION			
SUBTOTAL:			1675€
TOTAL AMOUNT:			15,683.63€

14.IMPACT

MRONJ is a disabling disease that gets worse the quality of life of the patients that suffer it. Most of these patients are suffering from cancer and their life expectancy is short. So, for them, the quality of life is very important. If this new treatment with surgery plus PRP can close the wound, eliminating infection, pain, teeth loses and bone exposure we will improve the quality of life of these patients. They will be able to eat, to smile and their social life will be easier. It is very important because there is no effective treatment for MRONJ yet. It will be a step forward in the treatment of this disease.

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16. ANNEXES

16.1.ANNEX 1: INFORMATION SHEET

INFORMATION SHEET FOR PATIENTS

We are writing to you to inform and invite you to participate in a research study that is being held in the University Hospital of Girona Dr Josep Trueta. Before you decide whether or not you wish to participate in this study, it is important for you to understand the research is being done and what it will involve. Please take your time to read the following information carefully and ask us if there is anything that is not clear or if you would like more information.

VOLUNTEER COOPERATION

Participation in this study is totally voluntary. If you decide to participate you will be asked to sign a consent form. If you decide not to take part of the study it will not affect the standard of care you receive. Once you are in the study you can withdraw your consent in any moment.

PURPOSE OF THE STUDY

Our objective is to compare the effectiveness of the surgical treatment for Medication-Related Osteonecrosis of the Jaws (MRONJ) versus the addition to this surgical treatment of Platelet Rich Plasma (PRP). The treatment for this disease is not standardized. With conservative measures we have seen that the response rate is very low. The surgical treatment has shown better results, but it is still not enough, because there is a high rate of dehiscence after the surgery. We suggest the application of PRP since its healing properties. Given the fact that the incidence of MRONJ is increasing

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because there are a lot of patients taking bisphosphonates, and taking into account that it causes a severe disability it is very important to find an effective treatment.

The study consists of a clinical trial with 2 groups of patients, the first group will be treated only with the surgical approach and the second group will be treated with the same surgical approach plus PRP. Once you are in the study you will be assigned randomly in one group. Randomization ensures the assignments of participants in one of the groups, having all of them the same probability of being assigned to one group or the other. The surgery will consist of the resection of the necrotic bone making an incision in the gum and performing curettage until healthy bone appears. All this will be done under local anaesthesia. Before starting the surgery, a nurse will draw blood from your vein and if you are in the PRP group this blood will be used to prepare the PRP and at the end of the surgery it will be injected around the wound. If you are not in the PRP group, this blood will be properly eliminated.

CONFIDENTIALITY

The information that we collect for this research project will be kept confidential in accordance with the Organic Law of Data Protection (15/1999). The data will be used only for the purposes of this study. Any information about you will have a number on it instead of your name.

Thank you for reading this.

**If you agree to enter the study, please sign the
attached consent form and we will return a copy to you.**

16.2.ANNEX 2: INFORMED CONSENT

CONSENT FORM

Project: Surgery alone vs surgery plus PRP in the treatment of Medication-Related Osteonecrosis of the Jaws. A clinical trial.

1. I confirm that I have read and understood the information sheet of the study.
2. I understand that my participation is voluntary and that I am free to withdrawal at any time without giving any reason, keeping my medical care and legal rights.
3. I give permission to study researchers and collaborators to have access to my medical notes and data collected during the study.
4. I agree to take part in this study.

Participant's name

Date

Signature








Doctor' name

Date

Signature

16.3.ANNEX 3: VAS PAIN SCALE

How severe is your pain today? Place a vertical mark on the line below to indicate how bad you feel your pain is today.

0	1	2	3	4	5	6	7	8	9	10
										
No pain		Mild, annoying pain		Nagging, uncomfortable, troublesome pain		Distressing, miserable pain		Intense, dreadful, horrible pain		Worst possible, unbearable, excruciating pain

16.4. ANNEX 4: SF-36 QUESTIONNAIRE FOR QUALITY OF LIFE

Name: _____ **Ref. Dr:** _____ **Date:** _____

ID#: _____ **Age:** _____ **Gender:** M / F

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

Compared to one year ago, how would you rate your health in general now?

- ☐ Much better now than one year ago
- ☐ Somewhat better now than one year ago
- ☐ About the same
- ☐ Somewhat worse now than one year ago
- ☐ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

☐ Yes, Limited a lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

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Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Lifting or carrying groceries

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing several flights of stairs

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Climbing one flight of stairs

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bending, kneeling, or stooping

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking more than a mile

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking several blocks

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Walking one block

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

Bathing or dressing yourself

☐ Yes, Limited a Lot ☐ Yes, Limited a Little ☐ No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

☐ Yes ☐ No

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Accomplished less than you would like

☐ Yes

☐ No

Were limited in the kind of work or other activities

☐ Yes

☐ No

Had difficulty performing the work or other activities (for example, it took extra effort)

☐ Yes

☐ No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

☐ Yes

☐ No

Accomplished less than you would like

☐ Yes

☐ No

Didn't do work or other activities as carefully as usual

☐ Yes

☐ No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

☐ Not at all

☐ Slightly

☐ Moderately

☐ Severe

☐ Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

☐ None

☐ Very Mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you been a very nervous person?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?

- ☐ All of the time
- ☐ Most of the time

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- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt calm and peaceful?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Did you have a lot of energy?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

Have you felt downhearted and blue?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good Bit of the Time
- ☐ Some of the time
- ☐ A little bit of the time

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☐ None of the Time

Did you feel worn out?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Have you been a happy person?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

Did you feel tired?

☐ All of the time

☐ Most of the time

☐ A good Bit of the Time

☐ Some of the time

☐ A little bit of the time

☐ None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- ☐ All of the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the Time

GENERAL HEALTH:

How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

I am as healthy as anybody I know

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

I expect my health to get worse

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false

My health is excellent

- ☐ Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false