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A pharmacological protocol for the management of medication-related osteonecrosis of the jaws: A randomized study

Submission date
29/06/2023

Recruitment status
No longer recruiting

Registration date
06/07/2023

Overall study status
Completed

Last Edited
06/08/2024

Condition category
Musculoskeletal Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Medication-related osteonecrosis of the jaws (MRONJ) is a challenging situation in clinics. Previous studies showed that pentoxifylline (PTX) combined with tocopherol was beneficial in patients with osteoradionecrosis, due to its antioxidant and antifibrotic properties. This study aims to evaluate the effect of PTX and tocopherol in patients with MRONJ.

Who can participate?
Female Stage I MRONJ patients with osteoporosis who had developed MRONJ after tooth extractions

What does the study involve?
The test group receives the pharmacological protocol with PTX and tocopherol (2 months pre-operatively and 6 months post-operatively). The control group has sequestrectomy operations (surgical removal of necrotic bone) without any pharmacological preparation. The main outcomes are clinical healing of the mucosa after 1 month and clinical and radiographic healing of the bone lesion at 6 months.

What are the possible benefits and risks of participating?
It is expected that in osteoporosis patients with Stage I MRONJ, the proposed pharmacological treatment with PTX and tocopherol will improve mucosal and bone healing rates and minimize relapses and complications, as compared to the control group.

The drugs used in the study are safe; pentoxifylline (PTX) is a methylxanthine derivate that was originally approved by the Food and Drug Administration (FDA) to treat peripheral artery diseases and has been used to treat complications related to fibrosis for over 20 years. PTX increases vasodilation and erythrocyte flexibility and reduces blood viscosity, which leads to an improvement in peripheral blood flow and tissue oxygenation. Tocopherols are organic chemical compounds consisting of various methylated phenols with beneficial effects. Tocopherols decrease tissue fibrosis, reduce inflammation, and have antioxidant effects that protect cell membranes from lipid peroxidation by reducing the free radical damage generated during

oxidative stress. PTX in combination with tocopherol has a synergistic effect and is used for the management of osteoradionecrosis, with beneficial antioxidant and antifibrotic properties. The main risk for participants receiving the pharmacological treatment is that it is ineffective, and the chance of developing relapses or worsening the disease after the intervention remains high. No other risks other than those commonly associated with surgical intervention (e.g. post-operative bleeding, pain, swelling, infection) are foreseen.

Where is the study run from?
Department of Oral Surgery and Maxillofacial Surgery, Francesco Miulli Regional Hospital, University of Bari (Bari, Italy), and Oral Med Care srl, Regional Dental Medical Centre of Oral Surgery and Maxillofacial Surgery (Bitonto, Italy).

When is the study starting and how long is it expected to run for?
June 2013 to January 2023

Who is funding the study?
Francesco Miulli Regional Hospital (Generale Regionale Francesco Miulli) (Italy)

Who is the main contact?
Dr. Gianluca Colapinto, colapinto.gianluca@virgilio.it
Prof. Massimo Del Fabbro, massimo.delfabbro@unimi.it

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Additional identifiers

Study information

Scientific Title
Effectiveness of a pharmacological protocol with pentoxifylline and tocopherol for the management of medication-related osteonecrosis of the jaws (MRONJ): A randomized study on 202 osteoporosis patients.

Study objectives
The aim is to verify that pharmacological treatment of preparation with pentoxifylline and tocopherol in patients affected by MRONJ and candidates for surgery, improves mucosal and bone healing rates compared to patients affected by MRONJ and candidates for surgery not undergoing pharmacological preparation.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 13/02/2014, Institutional Review Board of the Francesco Miulli Regional Hospital (Strada Prov. 127 Acquaviva – Santeramo Km. 4, 70021, 70021 Acquaviva delle Fonti BA, ACQUAVIVA delle FONTI, 70021, Italy; +39 (0)803054111; protocollo.miulli@legalmail.it), ref: 203077-13/02/2014

Primary study design
Other

Study design
Single-centre interventional randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Medication-related osteonecrosis of the jaws (MRONJ) in osteoporosis patients

Interventions
All patients are randomly divided into two groups, a test group and a control group, in a double-blind manner. The test group will receive the pharmacological preparation with pentoxifylline (600 mg x 2/day) and tocopherol (800 IU x 1/day) from 2 months before to 6 months after the surgical procedure, while the control group will directly receive the surgical procedure. The results will be evaluated and it will be verified whether the pharmacological preparation improves the results.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Pentoxifylline, tocopherol

Primary outcome(s)
1. Mucosal healing measured clinically by visual inspection at 1 week, 2 weeks, 1 month, 2, 6, and 12 months after the intervention
2. Bone healing measured clinically and radiographically through cone beam computed tomography (CBCT) 6 and 12 months after the intervention

Key secondary outcome(s)
The following secondary outcome measures will be observed yearly from 1 year up to 8 years:
1. Stability of mucosal and bone healing measured using clinical observation of the absence of inflammatory signs and maintenance of closure without bone exposure for mucosal healing, and radiographic assessment of healthy bone with normal structure, using cone beam computed tomography (CBCT)
2. Incidences of complications, such as abscess, mucosal fistula, and phlegmon, measured throughout all the study using clinical inspection and patient's reported complaints
3. Relapses occurring when mucosal healing has occurred, but bone healing does not occur, which can lead to two scenarios:
3.1. The mucosa reopens with exposure to underlying necrotic bone
3.2. The mucosa remains closed, but a small fistula is created where it is possible to probe the underlying unhealed necrotic bone measured using clinical and radiographic evaluation

Completion date
31/01/2023

Eligibility

Key inclusion criteria
Patients with osteoporosis and MRONJ stage I

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
202

Key exclusion criteria

1. Cancer patients with metastatic bone disease
2. Other stages of MRONJ

Date of first enrolment
01/08/2013

Date of final enrolment
01/11/2017

Locations

Countries of recruitment
Italy

Study participating centre
Department of Oral Surgery and Maxillofacial Surgery, of the Francesco Miulli Regional Hospital, University of Bari
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Study participating centre
Oral Med Care srl, Regional Dental Medical Centre of Oral Surgery and Maxillo-Facial Surgery
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Sponsor information

Organisation
Ospedale Generale Regionale Francesco Miulli

ROR
https://ror.org/03djvm380

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Ospedale Generale Regionale Francesco Miulli

Results and Publications

Individual participant data (IPD) sharing plan
Data analysed during the current study will be available upon request from Prof Massimo Del Fabbro (massimo.delfabbro@unimi.it)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		13/07/2023	06/08/2024	Yes	No