

Review
by
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**on a dissertation for the award of a
educational and scientific degree “Doctor“**

Author: Dr. Rosen Bozhidarov Tsholov

**Topic: „Treatment of medication-related osteonecrosis of the jaws with the
use of platelet rich fibrin PRF**

The thesis presented to me for review contains 180 standard typewritten pages with a bibliography consisting of 200 authors, of which 14 in Cyrillic script and 166 in Latin script, and 5 appendices. It is illustrated with 61 figures and 20 tables. The dissertation is well structured, which facilitated the review preparation.

The **Introduction** emphasizes the fact that at present, the treatment of medication-related osteonecrosis of the jaw surgical treatment remains one of the most reliable methods, but it must also undergo its modernization and benefit from advances in research. One of these achievements is the platelet-rich fibrin membrane (PRFm), which can be obtained in an easy and affordable way in an outpatient setting

The use of a PRF membrane as an adjunct to wound healing and periodontal regeneration has shown promising results. However, most studies with PRF show only short-term results. More controlled long-term clinical trials are needed to gain a deeper knowledge of the long-term efficacy and reliability of this biomaterial and to optimize its use in daily procedures.

The above facts give grounds for the candidate to formulate:

The aim of the dissertation: To make a comparative assessment of the results of conservative antibiotic treatment and surgical treatment with platelet-rich fibrin membrane (PRFm) of medication-related osteonecrosis of the jaws.

The materials and methods of the study are correctly and adequately selected, the use of a sufficient number of modern **statistical methods** for processing the obtained data ensures that reliable and objective **results** are attained.

In order to meet the set aim, **4 tasks** have been formulated and completed.

First Task: Study of the frequency of medication-related osteonecrosis of the jaws in Bulgaria.

Material on the first task

The study of the frequency of medication-related osteonecrosis of the jaws (MRONJ) in Bulgaria and the used treatment methods are provided by the National Health Insurance Fund (NHIF). The data are presented in spreadsheets in Excel, which show the number of patients with MRONJ by year in the period 2015-2018, as well as the specific drugs with which the patients were treated.

Statistical methods

The frequency of medication-related osteonecrosis of the jaw in the period 2015-2018 is presented in number and percentage change. Fisher's test was used to statistically compare the distribution of MRONJ to the drugs used.

The **results** obtained show that:

1. The frequency of MRONJ in Bulgaria in the period 2015-2018 increases annually to 8.5%, which is in accordance with the norms established in other studies and adopted by the American Association of Dentists and Maxillofacial Surgeons.
2. There is a strong trend of statistical significance of MRONJ and ibandronic acid treatment. The incidence of this treatment is 92% of all cases.

Materials on the second, third and fourth task

Place of study

The clinical trial was conducted in the clinical halls of St. George University Hospital. The period was from January 2013 to December 2017.

Materials

The study includes a total of 237 people who underwent the clinic of maxillofacial surgery “St. George” in the period 2013-2017. Of these 130 are women and 107 are men.

Patient selection criteria

Included criteria

- ☒ Established bisphosphonate osteonecrosis.
- ☒ Patients must be 18 years old or older.

Excluded criteria

- ☒ Presence of immunodeficiency.
- ☒ Patients taking anticoagulants and antiplatelets.
- ☒ Patients on steroid therapy for more than 10 days.
- ☒ Pregnant women with contraindications for surgical interventions.
- ☒ Presence of allergy to medications used during treatment.
- ☒ Presence of ulcerative colitis and enteritis.
- ☒ Established diseases of the liver and kidneys.
- ☒ Patients smoking more than 10 cigarettes a day or taking drugs.

Methods on the second, third and fourth task

1. **Diagnostic methods**-anamnesis

2. **Clinical methods**-clinical evaluation:redness, presence of edema, presence of healthy granulation tissue, signs of epithelialization

3. **Paraclinical methods**

- ✚ x-ray evaluation
- ✚ radiological symptoms
- ✚ laboratory studies

4. **Medicinal methods**

- ✚ conservative treatment; antibiotic treatment, local antiseptic therapy, pain control
- ✚ surgical treatment with platelet-rich fibrin (PRF)

The surgical treatment of the patients from the PRF group was performed according to the following protocol:

- ❖ cleaning the operative field.
 - ❖ applying anesthesia.
 - ❖ preparation of mucoperiosteal flap.
 - ❖ excision of the osteonecrotic lesion.
 - ❖ placement of PRF.
 - ❖ placing a suture.
- ⚡ technique for making the PRF membrane
- ⚡ postoperative care of the group with PRF treatment

Second Task: Study of the peculiarities of the radiological symptoms in bisphosphonate-induced osteonecrosis of the jaws.

The **results** obtained show that:

- 1) A similar topographical and anatomical localization is established in the two types of treatment, without significant difference.
- 2) Regarding the size in patients with PRF treatment - a higher percentage of patients with a size of ≤ 1 mm is observed. The majority of patients in the PRF treatment group were in the first two size categories: ≤ 1 mm and $> 1 - 3$ mm. The majority of patients on conservative treatment are $> 1 - 3$ mm and $> 3 - 5$ mm in size.
- 3) PRF treatment is characterized by a significantly higher percentage of patients with strong shadow intensity, while conservative treatment is dominated by the percentage of low intensity.
- 4) Regarding homogeneity - in PRF treatment homogeneity and sequestration dominate, and no heterogeneity occurs. In conservative treatment, the percentage of homogeneity and sequestration is lower and inhomogeneity is also found.
- 5) In patients on PRF treatment, sharp and continuous outlines predominate, while in patients on conservative treatment, blurred and interrupted outlines are more common.
- 6) A change in the surrounding bone is found in patients on conservative treatment and is not observed in patients on PRF treatment.

Third Task: Comparative radiological evaluation of the results obtained after treatment of medication-related osteonecrosis of the jaws, conservatively (medically) and surgically with the help of PRF.

The **results** obtained show that:

1) In both types of treatment, the values of osteolysis are similar and change in a similar way - they decrease significantly until the 30th day, then there is an increase on the 90th day, but the values on the 90th day are lower than those before treatment and on the 14th day.

2) The bone density of the two groups was similar before treatment, but over time significantly higher values were observed in the PRF-treated group. In addition, the change in bone density values showed different trends in the two types of treatment. In the PRF group there is a gradual increase, with the highest value reported on the 90th day. In the conservative treatment group, the mean bone density decreased and on the 90th day the lowest value was observed.

3) The buccal width is higher in the PRF group on the 45th day, but on the 90th day the trend changes and a higher value is reported in patients with conservative treatment. Intra-group change follows different directions in both types of treatment. PRF treatment showed a decrease in the mean between the 45th and 90th day, while in the conservative treatment the mean values between the two measurements increased.

4) Lingual width has significantly higher values in the PRF group and changes differently in both types of treatment. In PRF treatment, a decrease in width was observed between the 45th day and the 90th day, and in conservative treatment there was an increase between the two time points.

Fourth Task: Comparative clinical evaluation of the results obtained after treatment of medication-related osteonecrosis of the jaws, conservatively (medically) and surgically with the help of PRF.

The **results** obtained show that:

1) In both types of treatment there is a significant reduction in the percentage of patients with redness between the intervention and on the 90th day, but in PRF treatment the reduction occurs faster and is statistically greater than that of the group of conservative treatment.

- 2) The development of edema shows a similar trend in both types of treatment. From 100% after the intervention, the presence of edema decreases to 0% on the 90th day. At individual time points, no significant difference was found in the development of the two groups, except on the 14th day, when a greater reduction occurred in the PRF group.
- 3) The development of healthy granulation tissue is similar in both treatments: It occurs on the 7th day in the majority of patients and up to the 30th day in all patients, regardless of treatment.
- 4) The development of signs of epithelialization differs in the two types of treatment. In the PRF group, development was rapid and by the 14th day, all patients showed signs of epithelialization. In the group with conservative treatment the development is slower and gradual and does not reach 100%. On the 90th day, 13% of patients showed no signs of epithelialization.

The results of the research give the doctor reason to draw the following important **implications:**

Original and scientifically applicable contributions:

1. For the first time in Bulgaria a study of the frequency of MRONJ and the bisphosphonates used for the treatment of patients is made.
2. The present study is the first in Bulgaria to use a platelet-rich fibrin (PRFm) membrane for the treatment of MRONJ.
3. For the first time in Bulgaria a comparative clinical evaluation of the healing ability of the membrane of platelet-rich fibrin (PRFm) is made, in comparison with the conservative method of treatment of MRONJ.
4. For the first time in Bulgaria a comparative radiological assessment is made for the possibilities for bone density and regeneration of the membrane from platelet-rich fibrin (PRFm), in comparison with the conservative method of treatment of MRONJ.
5. For the first time in Bulgaria the author makes a comparative computer-topographic study of the possibilities for complete long-term healing of the membrane of platelet-rich fibrin (PRFm), compared to the conservative method of treatment of MRONJ.

Assessment of publication activity

In connection with the dissertation, **Dr. Rosen Tsholov** presents 3 publications. This fact proves that the topic developed in the dissertation is his personal work.

The author's summary objectively reflects the dissertation. It is drawn up in accordance to the requirements of the law for the development of the academic staff.

I have no critical remarks on the reviewed thesis.

Conclusion:

The thesis of **Dr. Rosen Bozhidarov Tsholov** is an in-depth study about treatment of medication-related osteonecrosis of the jaws with the use of platelet rich fibrin PRF.

The obtained results are valuable for clinical practice and can serve as a basis for future research.

I am confidently giving my positive vote for **the award of a educational and scientific degree "Doctor" to Dr. Rosen Bozhidarov Tsholov**

Plovdiv
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(Prof. Yavor Kalachev, DMD, PhD)