

Personal standpoint

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on the dissertation for awarding the educational and scientific degree "Doctor",
professional field 10.05.21 Surgical dentistry

Author: Dr. Rosen Bozhidarov Tsolov

Form of doctoral studies - full-time doctoral studies

Department of Oral Surgery, SPF at MU - Varna

Topic: "Treatment of medication-related osteonecrosis of the jaws with the use of platelet-rich fibrin prf"

Supervisor: Prof. Tihomir Dobrinov Georgiev, MD, PhD, Medical University - Varna, SPF, Department of Oral Surgery

I. General presentation of the procedure and the PhD student

The presented set of materials on paper / electronic media (including dissertation, abstract, administrative package of documents) is in accordance with Art. 24, para. 6, and Art. 30 of Rules For Implementation Of The Law On The Development Of The Academic Staff In The Republic Of Bulgaria /RILDASRB/, paragraph 5 of the Regulations for the development of the academic staff in MU - Varna.

The doctoral student has also attached a list of activities in connection with the dissertation. The documentation prepared by Dr. Rosen Tsolov is diligently and correctly prepared and meets the requirements of MU - Varna.

II. Brief biographical data about the doctoral student

Dr. Rosen Tsolov was born on April 21, 1980 in the city of Plovdiv. During the period 1999 - 2005 he studied at FDM - MU Plovdiv and acquired the specialty of Dentist. Since 2006 he has been working at the University Hospital "St. Georgi EAD, Plovdiv, Clinic of Oral and Maxillofacial Surgery. He has three participations as an author of scientific publications.

III. Relevance on the subject and the expediency of the set goals and objectives

The topic chosen by the doctoral student is clinically significant and dissertable.

The Introduction to the dissertation presents the surgical treatment of drug-induced osteonecrosis of the jaw as one of the most reliable therapeutic methods. Emphasis is placed on the need to update it. A modern method is the membrane of platelet-rich fibrin (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 is a method that 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 efficacy and reliability of this biomaterial and to optimize its use in day-to-day procedures.

The above facts give grounds for the doctoral student to formulate:

The aim of the dissertation work: To make a comparative evaluation of the results of conservative antibiotic treatment and surgical treatment with platelet-rich fibrin membrane (PRFm) of drug-induced bone necrosis of the jaws. The goal is formulated concisely and clearly, the most synthesized is indicated on what the activities in the present study will focus on.

IV. Literature review

The literature review includes four major points in which the etiology and pathogenesis of medication-related osteonecrosis of the jaws (MRONJ) are examined in detail. Particular attention is paid to the methods of treatment of MRONJ. A critical analysis of the therapy techniques used worldwide and in Bulgaria has been made, and the therapy with platelet-rich fibrin of MRONJ is presented in detail.

The bibliography includes 200 literary sources - 14 in Cyrillic and 186 in Latin, with the predominance of scientific works from the last 10 years.

Analysis of the review shows that the PhD student is fully familiar with the issue and can discuss creatively and freely cited data and facts from the literature. The review is written in correct Bulgarian and has a good scientific style.

V. Research methodology

The material and methods of the research are correctly selected, the use of a sufficient number of modern **statistical methods** for processing the obtained data guarantees the receipt of reliable and objective results. In order to fulfill the set goal, **4 tasks** have been formulated and completed.

First task: Study of the frequency of MRONJ in Bulgaria.

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

Third task: Comparative radiological evaluation of the results obtained after treatment of drug-induced bone necrosis of the jaws, conservatively (medically) and surgically with the help of PRF.

Fourth task: Comparative clinical evaluation of the results obtained after treatment of drug-induced bone necrosis of the jaws, conservatively (medically) and surgically with the help of PRF.

Material on the first task

The study of the frequency of MRONJ in Bulgaria and the treatment methods used is based on official data 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 incidence of MRONJ in the period 2015-2018 is presented in number and percentage change. Fisher's test was used for the statistical comparison of the distribution of MIONCH with the used drugs.

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. 92% of all cases were due to treatment with ibandronic acid.

Materials for second, third and fourth task

Place of study

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

Material

The study included 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

Including criteria

- Established bisphosphonate osteonecrosis.
- Patients must be 18 years of age or older.

Excluding 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 for second, third and fourth tasks

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 researches

4. Treatment methods

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

Surgical treatment of patients in the PRF group was performed according to the following protocol:

- cleaning the operating field.

- anesthesia.
 - preparation of mucoperiosteal flap.
 - excision of the osteonecrotic lesion.
 - placement of PRF.
 - stitching.
- technique for making 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 anatomical and topographic localization is established in the two types of treatment, without significant difference.
2. In terms of size, PRF treatment has a higher percentage of patients with a size of ≤ 1 mm. The majority of the PRF group are 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. In terms of homogeneity, homogeneity and sequestration dominate in PRF treatment, while heterogeneity does not occur. 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 drug-induced bone necrosis of the jaws, conservatively (medically) and surgically with the help of PRF.

The results obtained show that:

1. The values of osteolysis in both types of treatment are similar and change in a similar way - they decrease significantly until the 30th day, after which there is an increase on the 90th day, but the values on the 90th day are lower of those before treatment and on the 14th day.
2. The bone density of the two groups was similar before treatment, but in the process of time significantly higher values than were observed in the PRF 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 day 45, but on day 90 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 days 45 and 90, while in 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 day 45 and day 90, 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 drug-induced bone necrosis 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 day 14, when a greater decrease occurred in the PRF group.

3. The development of healthy granulation tissue is similar in both treatments: It occurs on day 7 in the majority of patients and up to day 30 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 day 14, all patients showed signs of epithelialization. The development is slower and gradual in the conservative group and does not reach 100%. On day 90, 13% of patients showed no signs of epithelialization.

VI. Characteristics and evaluation of the dissertation

The dissertation was carried out and written in accordance with the requirements of the Law On The Development Of The Academic Staff In The Republic Of Bulgaria (LDASRB) and the Regulations for its implementation, as well as the Regulations of MU - Varna. It is prepared according to all requirements and is written in good literary language and in a professional style. The whole work is perfectly illustrated with very good scans, correctly presented tables, diagrams, and there is a very good statistical processing. I find the ideas implemented in the dissertation interesting, some even original, which increases its scientific significance.

Structure of the dissertation

The dissertation presented to me for review contains 180 standard typewritten pages with a bibliography of 200 authors, of which 14 in Cyrillic and 166 in Latin and 5 appendices.

It is illustrated with 61 figures and 20 tables. The dissertation is developed and structured according to all necessary requirements.

Conclusions.

The conclusions are 9 (nine) and are given separately in a special section and logically follow from the research. Together with the conclusion, they can also be considered as addressed to the practice of dentists.

VII. Contributions and significance of development

Five contributions of original scientific and applied nature are indicated, which I fully accept. **Originality and creativity.**

The doctoral student has made visible efforts to have a level of independence and originality in the dissertation.

VIII. Assessment of publication activity

In connection with the dissertation, Dr. Rosen Tsolov presents 3 full-text articles, of which he is the lead author.

IX. Abstract.

The abstract is made according to the normative requirements and is an objective reflection of the dissertation. It clearly and clearly presents the work in a reduced form, reflecting all the important points of the dissertation, in addition, the contributions of the dissertation are added.

X. Critical remarks and recommendations

I have no critical remarks and recommendations for the dissertation written in this way.

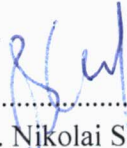
XI. Conclusion:

The dissertation contains scientific-theoretical and applied results, which represent an original contribution to science and meet the requirements of LDASRB, the Regulations for its application and the relevant Regulations of MU - Varna.

The dissertation shows that the doctoral student Dr. Rosen Bozhidarov Tsolov has in-depth theoretical knowledge and professional skills in the scientific specialty of Surgical Dentistry, demonstrating qualities and skills for independent research. Due to the above, I confidently give my positive assessment of the study presented by those reviewed above.

Due to the above, I confidently give my positive assessment of the research presented by the above dissertation, abstract, results and contributions, and I suggest the esteemed scientific jury to award the educational and scientific degree "Doctor" to Dr. Rosen Bozhidarov Tsolov.

Plovdiv
April 13, 2021


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(Assoc. Prof. Dr. Nikolai Sirakov, MD)