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TREATMENT OF MEDICATION-RELATED OSTEONECROSIS OF THE JAWS WITH THE USE OF PLATELIC RICH FIBRIN PRF

ABSTRACT

of a dissertation for the award of

educational and scientific degree "Doctor"

SCIENTIFIC SPECIALITY

10.05.2021

Supervisor:

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Varna, 2021

The Dissertation work was approved and directed for defence at a proceeding of Department of Oral surgery, Faculty of Dental medicine at Medical university “Prof. Dr. Paraskev Stoyanov” - Varna

The Dissertation work contains 180 standard printed pages and is illustrated with 30 tables и 90 figures. The literature consists of 200 sources, from which 14 in cyrilic and 166 in latin.

The public defence of the dissertation work is going to take place on 10.05.2021 from 12 o’clock in before a scientific jury composed of:

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LIST OF THE USED ABBREVIATIONS

AMP - Adenosine monophosphate

ATP – Adenosine triphosphate

BIONJ - Bisphosphonate-induced osteonecrosis of the jaw

MA – maxillofacial area

MC – mesenchymal cells

HA – hydroxyapatite

A-PRF – Advanced Platelet – Rich Fibrin

AAOMS – American Association of Oral and Maxillofacial Surgeons

BRONJ – Bisphosphonate-related osteonecrosis of the jaw

BPs – Bisphosphonates

HBO – Hyperbaric oxygenation

I-PRF – Injectable PRF

L-PRP – Leukocyte Platelet – Rich Plasma

L-PRF – Leukocyte Platelet – Rich Fibrin

MRONJ – Medication-related osteonecrosis of the jaw

PRP – Platelet-rich plasma

PRF – Platelet-Rich Fibrin

PRGF – Platelet-Rich Growth Fibrin

P-PRF – Pure Platelet-Rich Fibrin

P-PRP – Pure Platelet-Rich Plasma

RNS – Reactive nitrogen species

ROS – Reactive oxygen species

T-PRF – Titanium-prepared PRF

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is an area of open bone in the maxillofacial area that does not heal for more than 8 weeks and affects patients undergoing bisphosphonate drug therapy. These are mainly patients, which are with cancer and have undergone long-term intravenous treatment with bisphosphonates as part of the cancer therapy. The frequency of MRONJ worldwide is increasing along with the increase in prescribed bisphosphonates.

At present, the treatment of MRONJ remains a dilemma. Effective treatment has not yet been developed and the temporary cessation of bisphosphonates does not offer short-term benefits, while long-term discontinuation (if the systemic conditions allow it) may be helpful in stabilizing osteonecrosis sites and reducing clinical symptoms. The use of oral antimicrobial rinsing in combination with an oral systemic antibiotic - penicillin, metronidazole, quinolones, clindamycin, doxycycline, erythromycin - gives results only in the initial stage of treatment and can be used to stop the development of the disease, rather than to treat it.

Surgical treatment remains one of the most reliable methods, but it must also undergo its modernization and benefit from advances in research and the development of technologies that provide the opportunity for relatively easy and affordable use of new growth factors in maxillofacial surgery. 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 platelet-rich fibrin (PRF) in surgery is a new alternative method for the treatment of MRONJ. Dohan et al. (2006) developed a production protocol for PRF in an attempt to platelet aggregate and release cytokines in a fibrin clot. Platelets and leukocytes are an important part of this biomaterial, but the fibrin matrix that supports them is very useful in compiling the responsible determinants of the therapeutic potential of PRF.

The use of a PRF membrane as an adjunct to wound healing and periodontal regeneration has shown promising results. It is successfully used for correction of bone defects in periodontology, oral and maxillofacial surgery and implant dentistry. 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 goal of our study was 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 jaw.

I. GOALS AND TASKS

Goal: 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.

To achieve this goal, we set ourselves the following tasks:

First Task: Study of the frequency of medication-related osteonecrosis of the jaws 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 medication-related osteonecrosis of the jaws, conservatively (medically) and surgically with the help of PRF.

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.

II. MATERIALS AND METHODS

2.1. Materials

2.1.1 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.

2.1.2. Material on the first task

The study of the frequency of medication-related osteonecrosis of the jaws 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. The data from 2018 are only for the first half of the year, as the current survey was conducted at the end of the year, when the summarized annual data are not yet available.

2.1.3. Materials on the second, third and fourth task

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.

2.1.4. Patient selection criteria

2.1.4.1. Included criteria

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

2.1.4.2. 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.

2.2. Methods

2.2.1. Diagnostic methods

Diagnosing patients before performing manipulative interventions is key to determining the most appropriate method of treatment. The following diagnostic methods were used in the present study:

2.2.1.1. Anamnesis

In the relationship between us and patients, it was important to clarify and obtain as complete and accurate information as possible about the disease and the events that are directly related to it.

The taking of the anamnesis in the present study consists in asking questions to the patients in the group regarding the symptoms, the duration of their complaints, accompanying diseases, drug treatment, specific medication, their dosage and duration of administration, the presence of already performed surgical interventions, the presence of allergic reactions, daily habits such as smoking, etc.

2.2.2. Clinical methods

2.2.2.1. Clinical evaluation

After taking the anamnesis and the clinical examination, the patients are acquainted with the type and severity of their disease. An in-depth conversation was held and the various treatment options were discussed. Patients who have shown interest and confidence in surgical treatment are provided with additional information about the manipulation. Those who consented to surgical treatment signed an informed consent to participate in a clinical trial for the treatment of MRONJ with platelet-rich fibrin membrane - Appendix №5.

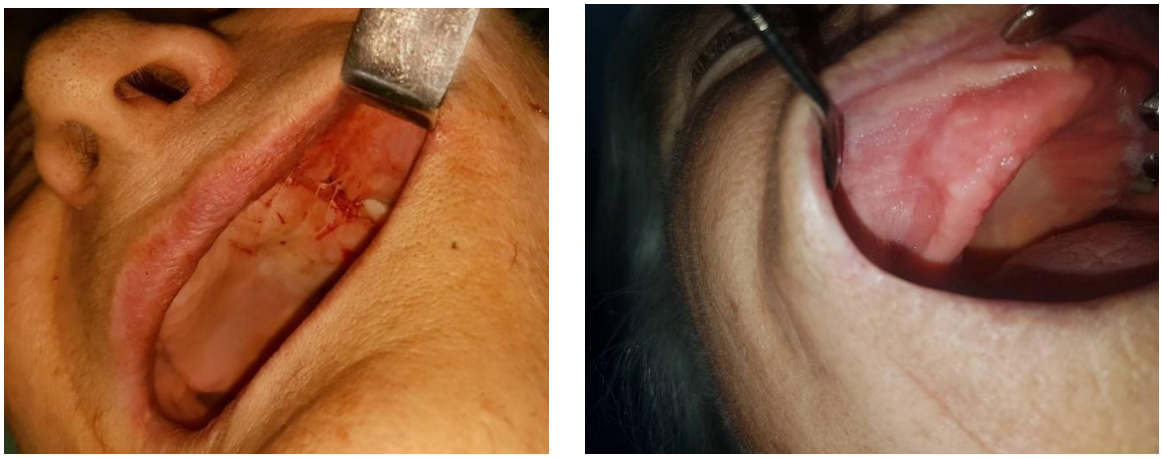
For the patients from the two treatment groups - surgically by PRF and conservatively (medically) we measured the selected clinical indicators for the study:

Redness – the presence of redness was checked in the following time ranges: first measurement - immediately after treatment (taking antibiotics for the group of conservative treatment and surgery of the group with a PRF membrane); second measurement - on the 7^{th} day; third measurement - on the 14th day; fourth measurement - on the 30^{th} day;

A **B**

Fig.1. Redness (A, B)

Presence of edema - we checked the presence of edema in the same time ranges: first measurement - immediately after treatment; second measurement – on the 7th day; third measurement - on the 14th day; fourth measurement - on the 30th day;



A **B**

Fig.2. Presence of edema (A, B)

Presence of healthy granulation tissue – the verification for the presence of healthy granulation tissue was also performed as follows: first measurement - immediately after treatment; second measurement - on the 7th day; third measurement - on the 14th day; fourth measurement - on the 30th day;

Signs of epithelialization – we verified the signs of epithelialization; first measurement - immediately after treatment; second measurement - on the 7th day; third measurement - on the 14th day; fourth measurement - on the 30th day; fifth measurement - on the 90th day;

A **B**

Fig.3. Signs of epithelialization (A, B)

2.2.3. Paraclinical methods

X-ray examination is the main method among paraclinical examinations of patients in the field of maxillofacial surgery. The method is based on the ability of different tissues to absorb X-rays to varying degrees.

2.2.3.1. X-ray evaluation

We performed the X-ray evaluation on the third task using a special extraoral method - orthopantomography.

Patients from both treatment groups - surgically by PRF and conservatively (medically) were measured for the selected clinical indicators as follows:

- **Osteolysis and bone loss -** measurements were performed: immediately after the intervention;

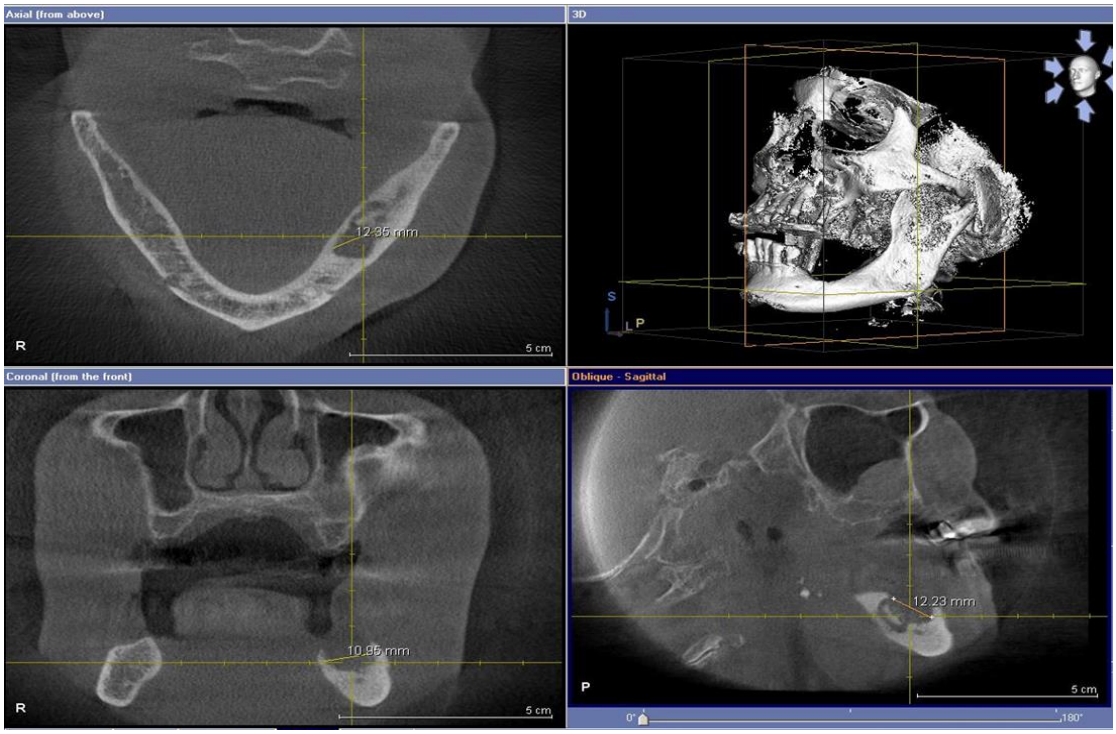


Fig. 4. Cross-sectional images in the three projection planes: a) axial; b) coronary; c) sagittal; d) 3D reconstruction. Measurements of sections with lytic changes, in mm.

- **Bone density –** measurements were performed: immediately after the intervention;

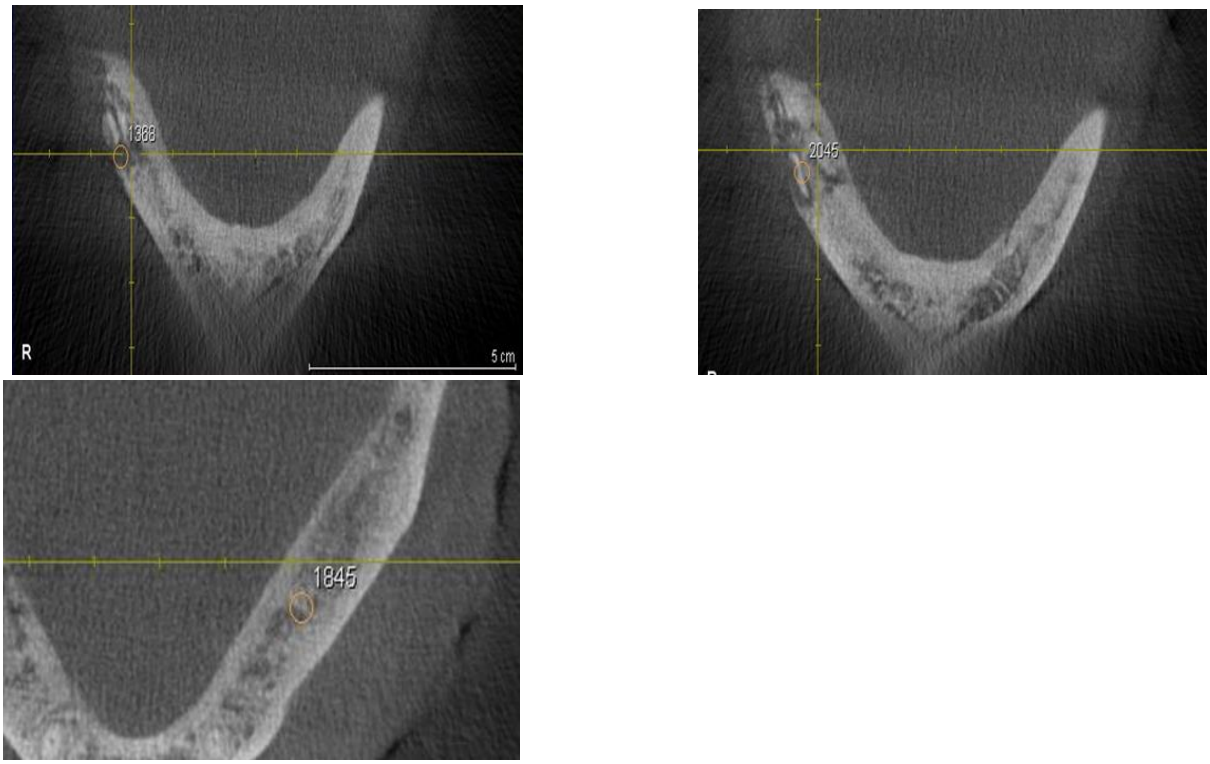


Fig. 5. Axial sections . ПDensity characteristic of: a) the normal structure of the bone spongiosa, symmetrical to the pathological processes of the lower jaw; b) the demineralized areas of the pathological processes; c) the sequesters;

- **Buccal width** – the measurements were performed: immediately after the intervention;

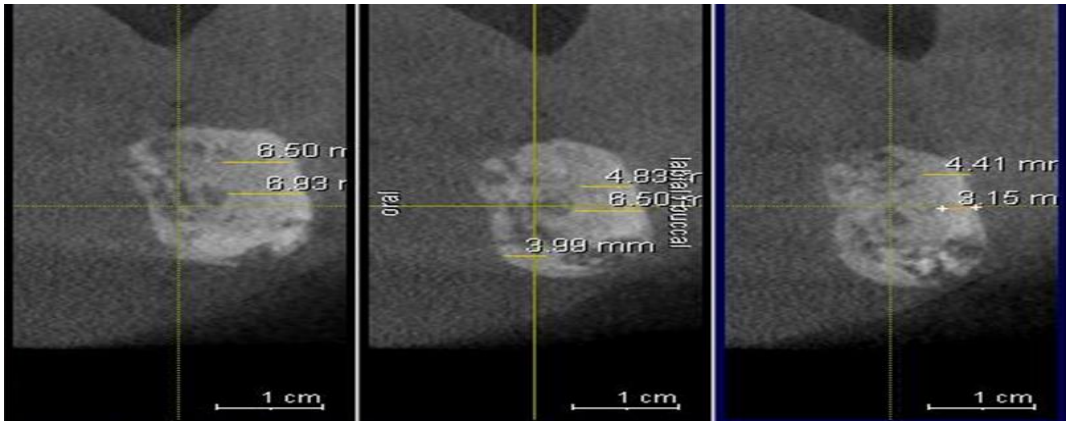


Fig. 6. Orthoradial (bucco-lingual) sections. Measurement of the width of the available lingual bone structure to the lesion.

- **Lingual width –** the measurements were performed: immediately after the intervention;

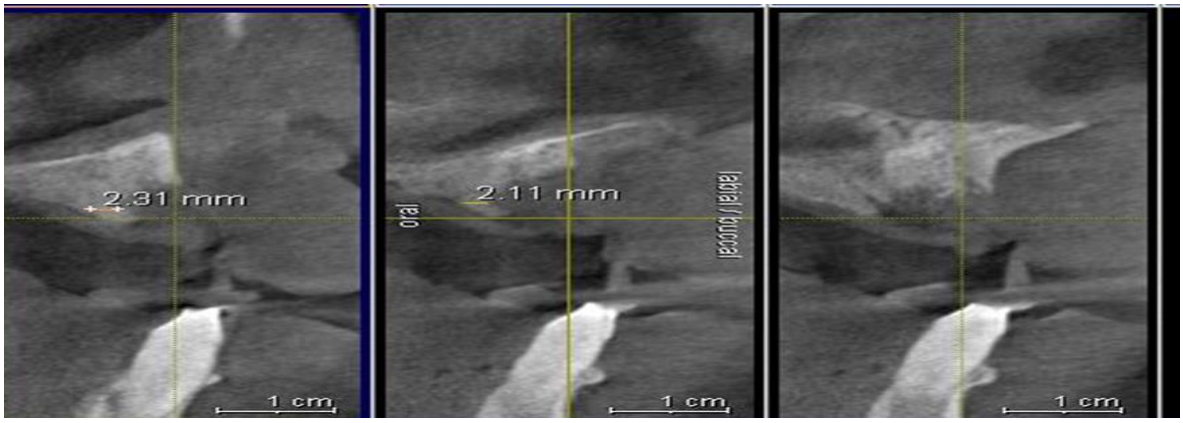


Fig.7. Orthoradial (buco-lingual) sections. Measurement of the width of the available lingual bone structure to the lesion.

2.2.3.2. Radiological symptoms

Study of the characteristics of the radiological symptoms in drug-induced osteonecrosis of the jaw we carried out on patients of both groups in the study six months after the treatment by non-invasive X-ray method of computer tomography. We measured the selected clinical indicators for the study:

- **Anatomical and topographic localization –** upper / lower jaw and left / right side.

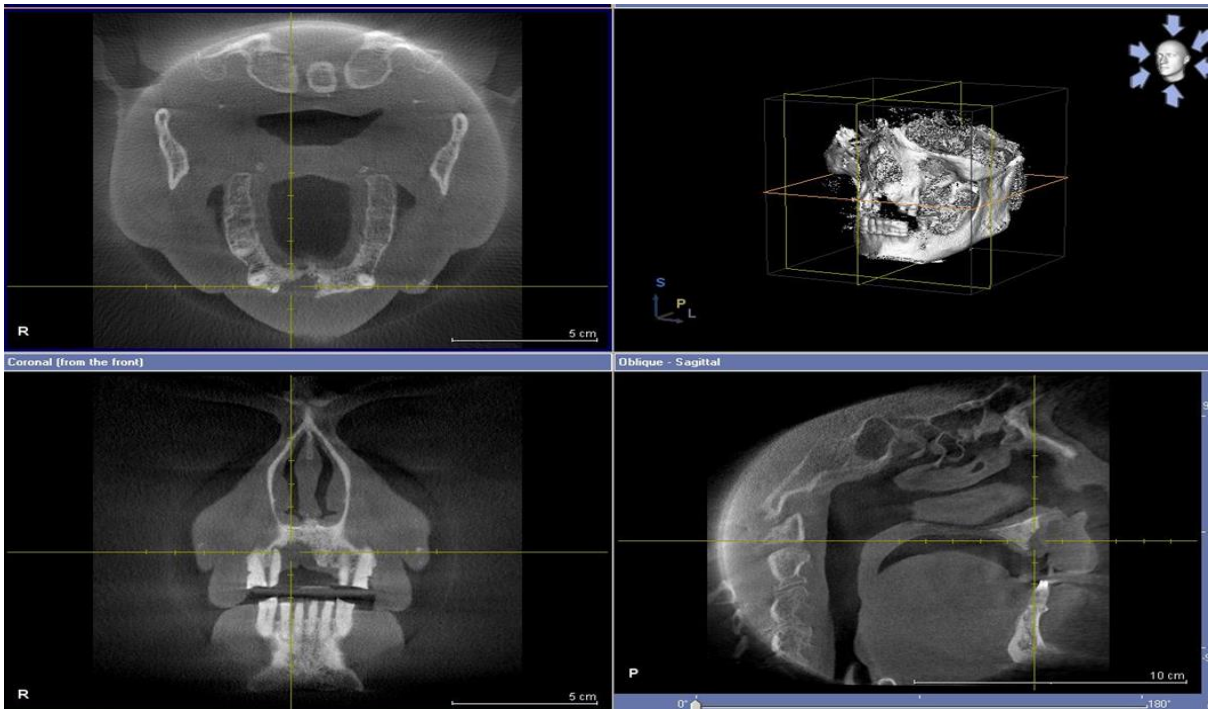


Fig.8. Cross-sectional images in the three projection planes: a) axial; b) coronary; c) sagittal; d) 3D reconstruction. Three - dimensional localization of the pathological processes - hypodense lesion in the area 11 and 12.

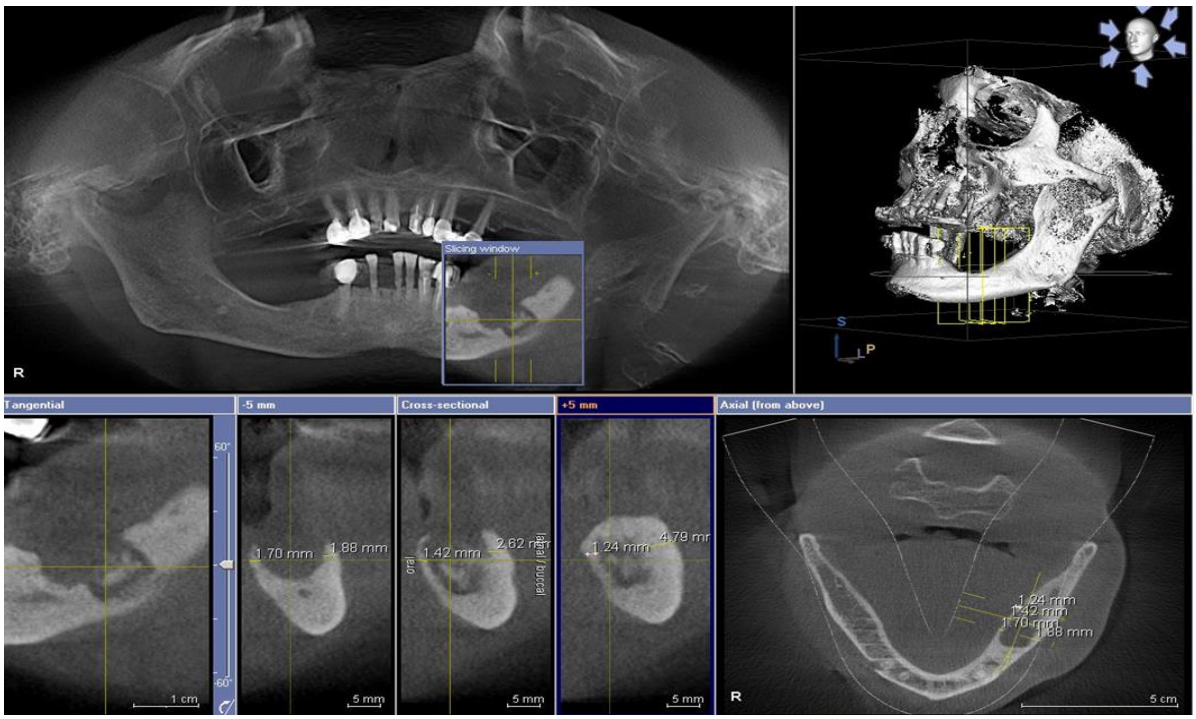


Fig.9. Panoramic reconstruction obtained after scanning, tangential, axial and orthoradial sections. Localization of pathological processes in the area of the molars of the lower jaw on the left.

- **Magnitude**– The magnitude of MRONJ was measured in millimeters.

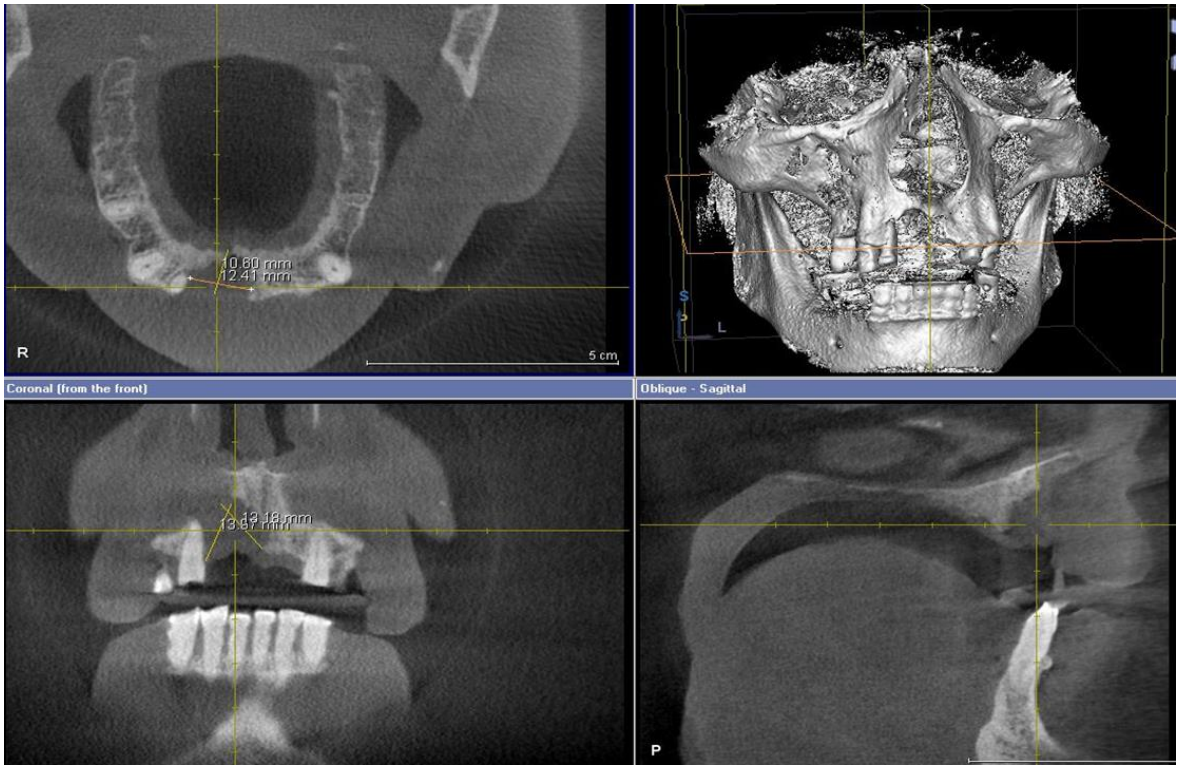


Fig.10. Cross-sectional images in the three projection planes and measurement of the magnitude of the MRONJ in millimeters.

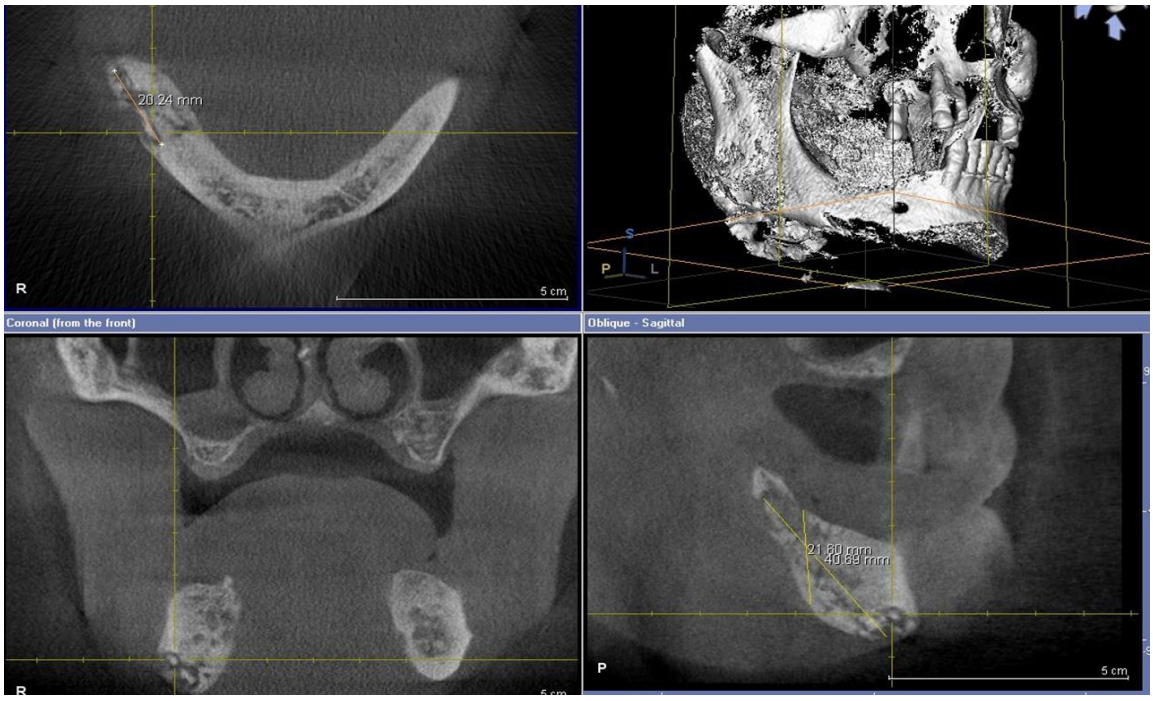


Fig.11. Cross-sectional images in the three projection planes and measurement of the magnitude of the MRONJ in millimeters.

- **Shadow intensity –** we used computed tomography to measure the intensity of the shadow - whether it is strong or weak.

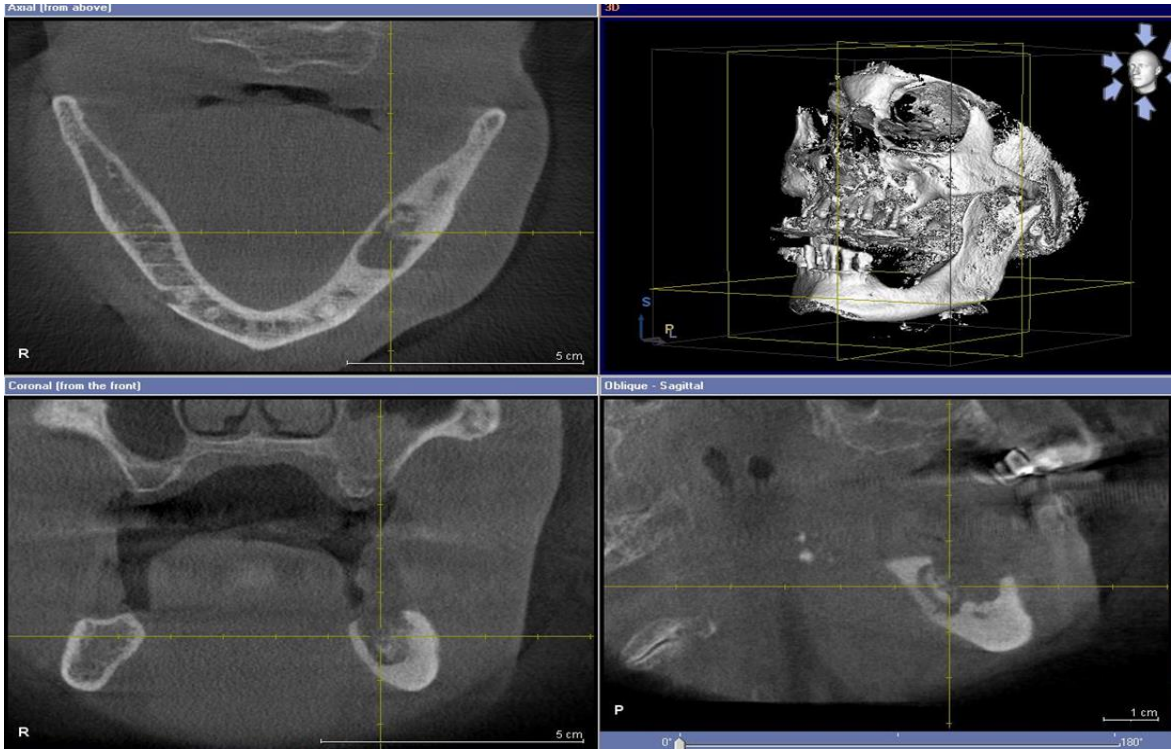


Fig.12. Cross-sectional images in the three projection planes: a) axial; b) coronary; c) sagittal; d) 3D reconstruction. Heterogeneity of the lesion and the presence of sequestration

- **Homogeneity –** in the control X-ray examination in the sixth month after treatment, we measured the homogeneity and in particular - its similarity and difference, as well as the presence of sequestration.

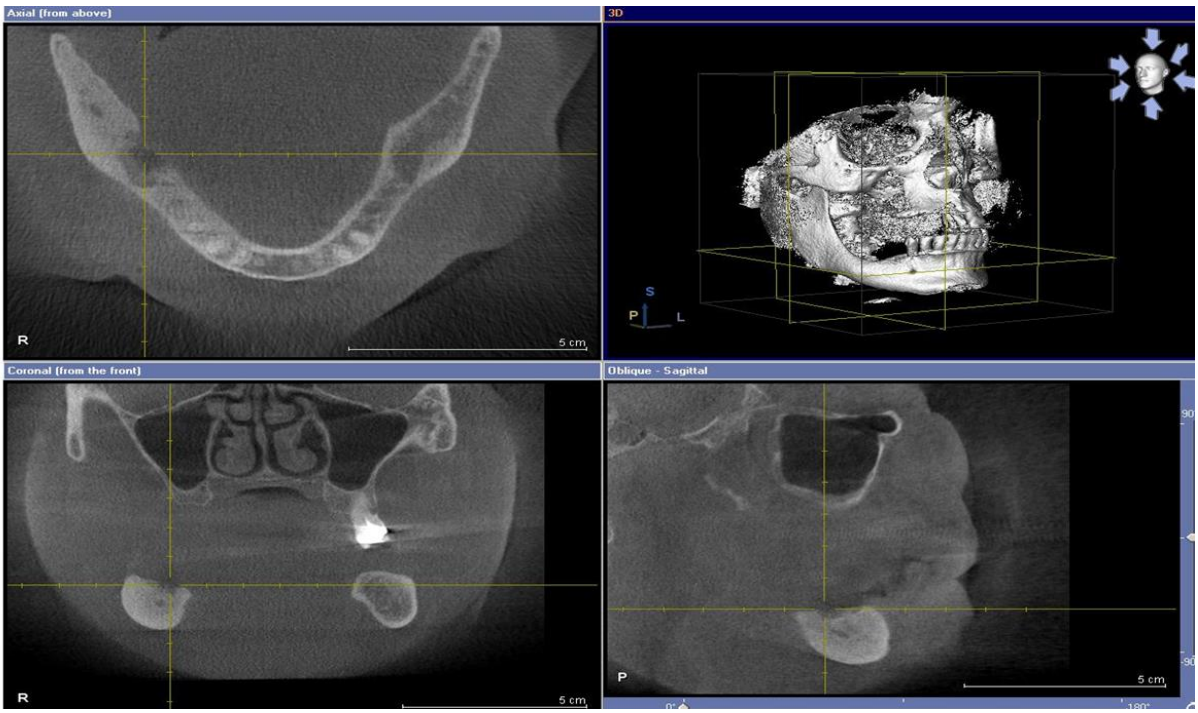


Fig.13. Cross-sectional images in the three projection planes: a) axial; b) coronary; c) sagittal; d) 3D reconstruction. Restorative changes.

- **Outlines –** we measured whether the outlines were broken or continuous, as well as whether they were sharp or unsharp.

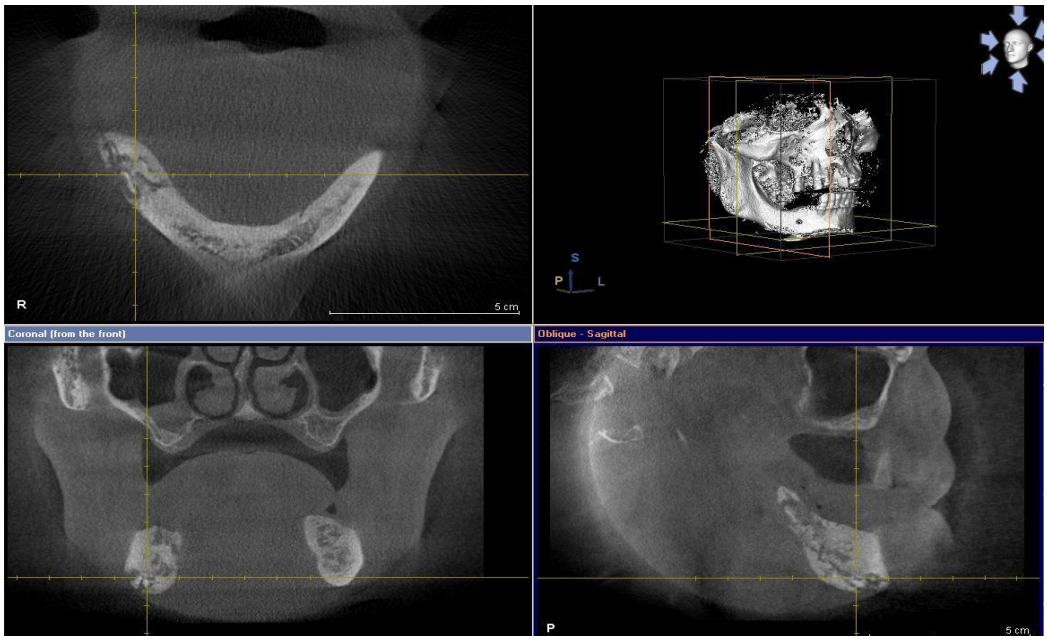


Fig.14. Cross-sectional images in the three projection planes: a) axial; b) coronary; c) sagittal; d) 3D reconstruction. Lesion of the lower jaw with blurred and uneven borders.

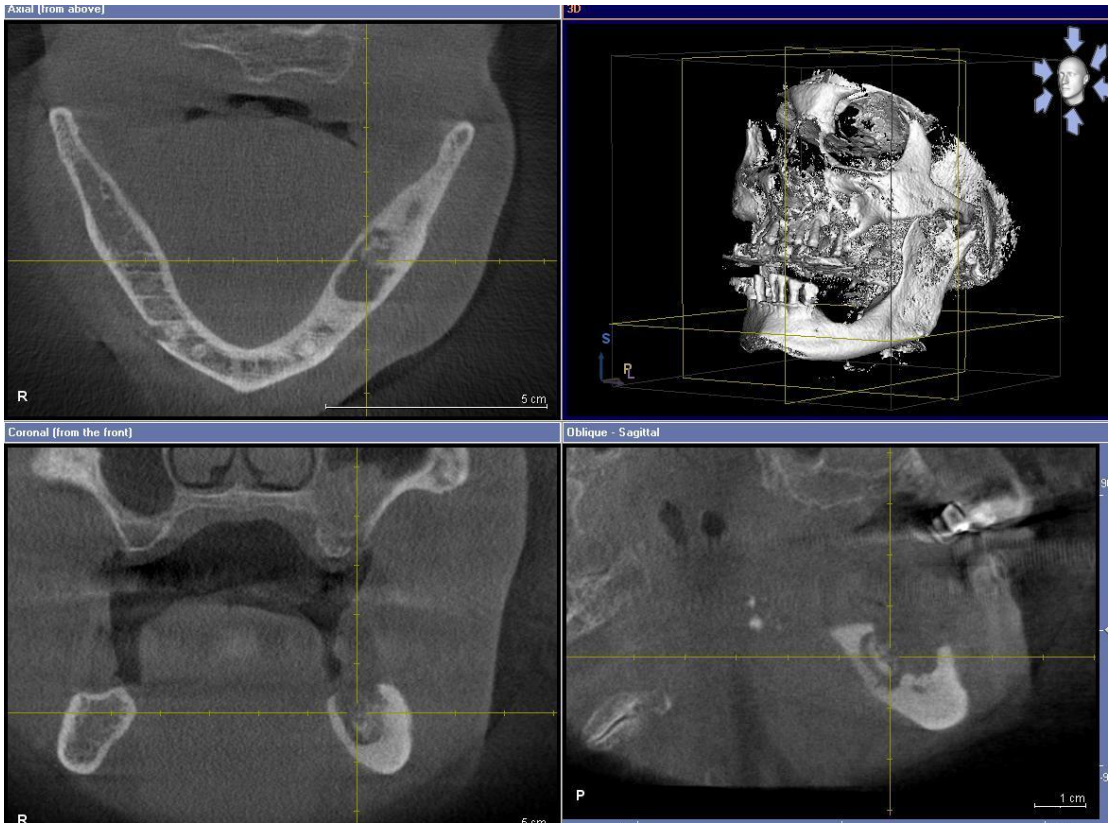


Fig.15. Cross-sectional images in the three projection planes: a) axial; b) coronary; c) sagittal; d) 3D reconstruction. Lesion of the lower jaw with sharp and smooth borders.

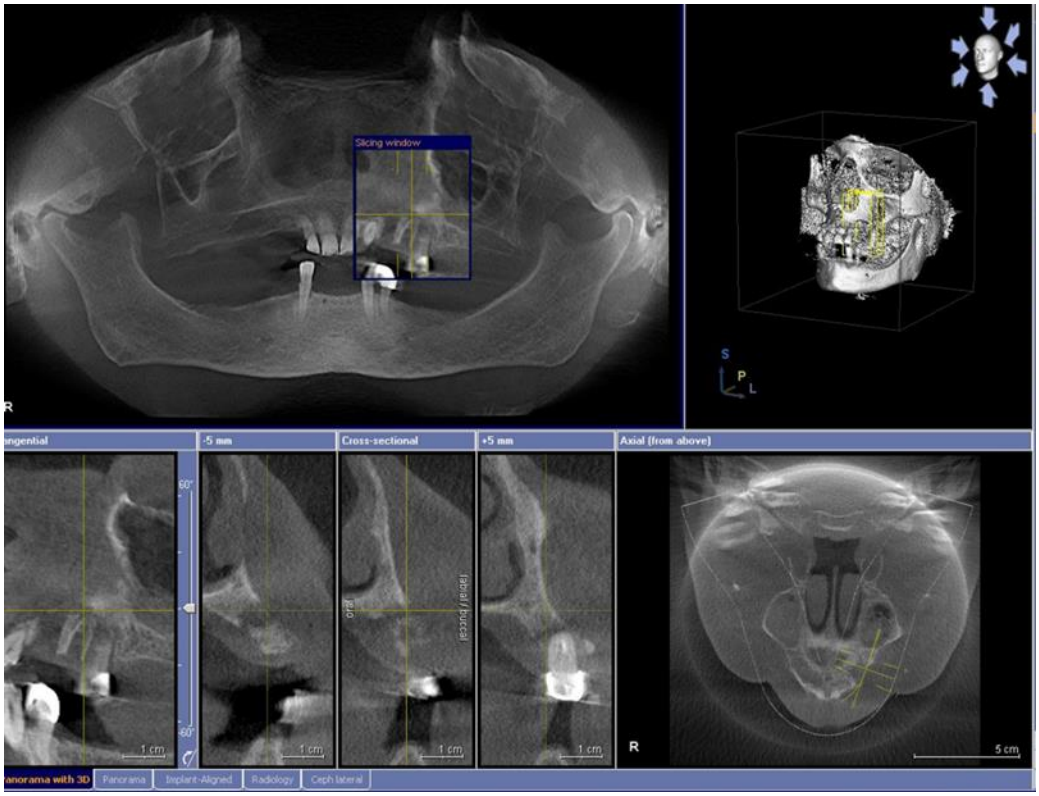


Fig.16. Control computed tomography at 6 months

2.2.3.3. Laboratory studies

All patients in the PRF treatment group were given laboratory blood tests before the intervention. Through these tests, we monitored the values of the peripheral blood picture, the time of bleeding and clotting. If necessary, we appointed additional tests and consultations.

Scope of the data

The patient data presented in this study include detailed information about their condition on admission to the clinic, the examinations and tests performed, the treatments performed and the achieved results based on them.

For the purposes of the study, a special card has been developed, in which all the listed data for each individual patient are filled in, which are integrated in the computer database and processed for the needs of the analysis / Appendix 1, 2, 3, and 4 /.

2.2.4. Medicinal methods

Once medication-related osteonecrosis of the jaw has begun, it becomes difficult to treat. The methods of treatment are conservative - the use of antibiotics and local antiseptics, physiotherapy and surgery - removal of necrosis. One of the most modern methods is bone

resection and assistance in the healing of soft tissues with a membrane of platelets rich in growth factors. [94]

We performed all treatment procedures after taking the anamnesis, conducting a clinical examination of the patients and evaluating some of the paraclinical results. Patients in the PRF surgical group were thoroughly interviewed and re-informed about the type, severity of their disease and the need for surgical treatment. All treatment methods and procedures used in the present study correspond to: Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects; The principles of the Good clinical practice; Bulgarian laws and regulations for conducting clinical and scientific research with the participation of people.

2.2.4.1. Conservative treatment

The first recommendations for the treatment of MRONJ with the help of drugs were given by the manufacturers of bisphosphonates, who recommended local and systemic antibiotic treatment, taking measures to improve oral hygiene and pain control.

The recommended antibiotics for the treatment of MRONJ are aminopenicillins, amoxicillin, metronidazole, fluoroquinolones, clindamycin, doxycycline, erythromycin.

Systemic antibacterial therapy is aimed at treating the infection and preventing the aggravation of the inflammatory process.

To the group of patients in our study, whom we treated conservatively, we applied all three stages in this method: antibiotic infusion; antiseptic therapy and pain control.

Antibiotic treatment - we performed with ampoules of clindamycin of 600 milligrams, lasting 5-7 days. Clindamycin was administered intravenously through a system, which we performed slowly due to the high risk of side effects harmful to the heart and blood pressure.

As soon as the anamnesis was taken, we identified the patients whom we refused treatment with clindamycin due to the presence of allergic reactions, ulcerative colitis, enteritis, liver and kidney diseases.

Immediately before starting treatment, we had another conversation with the patients, in which we reminded them of the possible side effects of taking the drug; what the effects and contraindications of actions and habits that they perform despite the explicit prohibition of the attending physician are, such as smoking and alcohol use, etc.

We warned them to let us know as soon as they felt their health deteriorating after taking the clindamycin solution.

Local antiseptic therapy is an important factor in the success of conservative treatment. It includes mouthwashes with chlorhexidine (chlorhexidine 0.12–0.2%).

Patients in the conservative treatment group in our study were assigned to rinse the oral cavity with 0.12% chlorhexidine solution three times a day for one minute for 20 days. Patients were also given saline iodine washes as well as oxygenated water. Flushing was performed by jet with syringes in the osteonecrotic lesion.

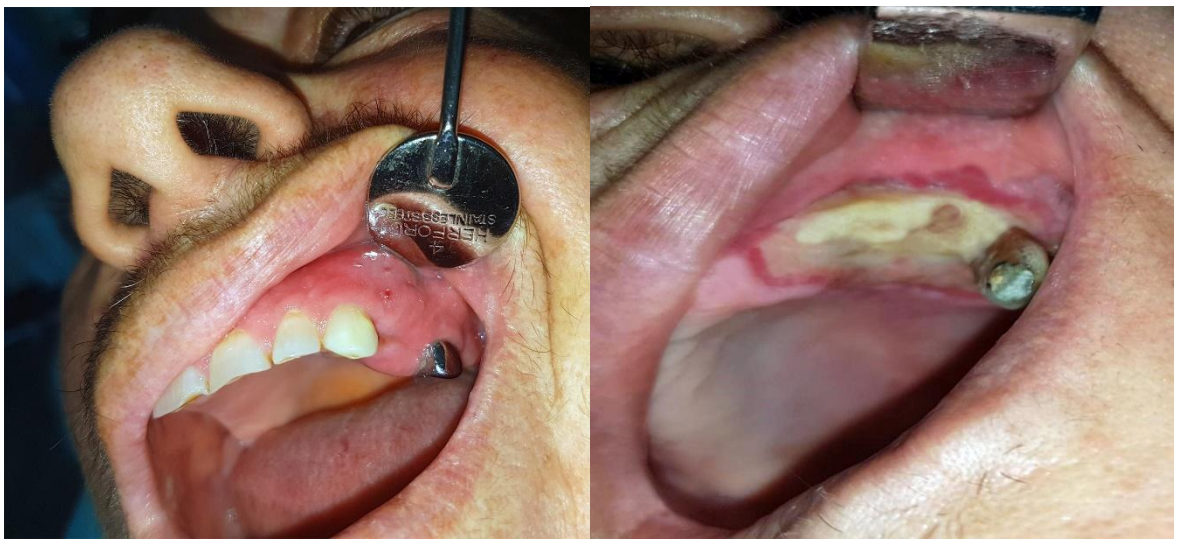
Pain control is necessary due to the presence of severe pain. In our conservative treatment, we gave all patients analgesics three times a day, which also have an anti-inflammatory effect.

2.2.4.2. Surgical treatment with platelet-rich fibrin (PRF)

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

1. Cleaning the operative field.
2. Applying anesthesia.
3. Preparation of mucoperiosteal flap.
4. Excision of the osteonecrotic lesion.
5. Placement of PRF.
6. Placing a suture.

The first step in surgical treatment is to clean the operating field with antiseptics. We cleaned with gauze soaked in iodasept.



A **B**

C **D**

E **F**

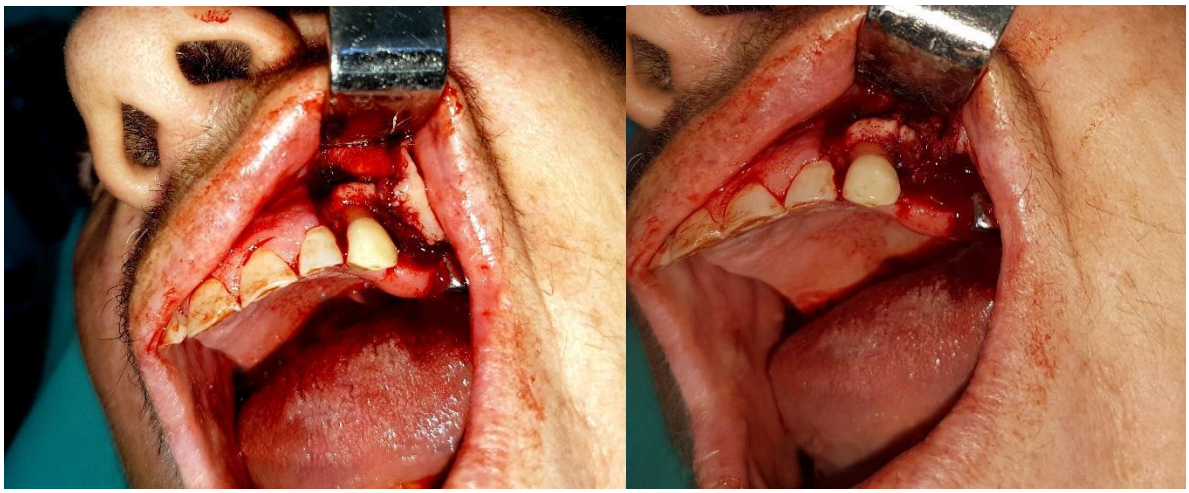
G

Fig.17. – Clinical manifestation of MRONJ (A, B, C, D, E, F, G)

After cleaning the operative field, we performed the necessary local anesthesia. In the area undergoing surgery, we injected local anesthesia with ubistesin 4%.

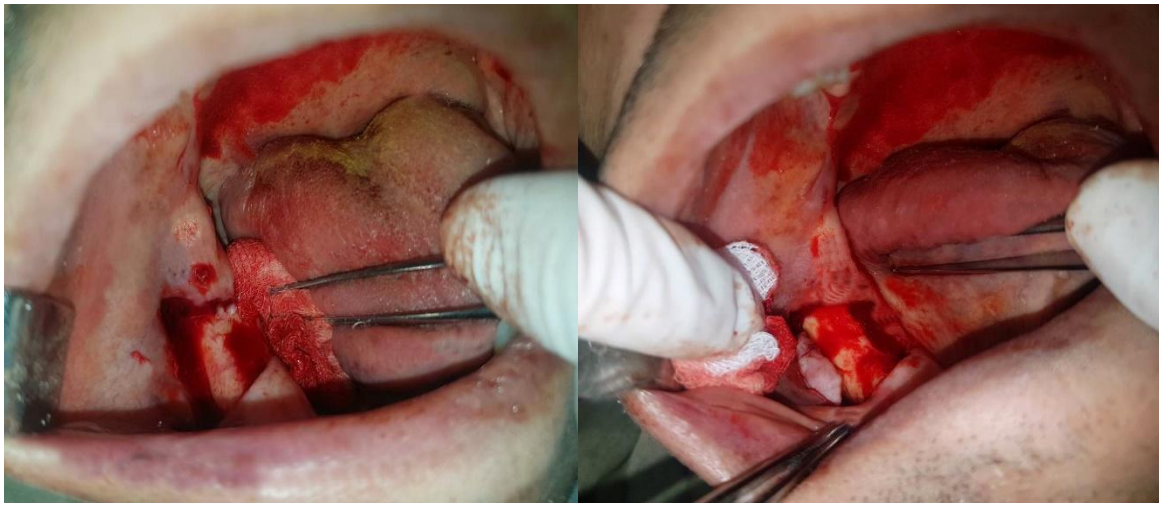
After the anesthesia was applied, the mucoperiosteal flap was dissected. With the help of a microsurgical handle for a scalpel and a blade №11 or №15, an incision is made (horizontal and vertical) of the mucosa, and the depth of the incisions reached the bone.

Depending on the location of the osteonecrotic lesion, a trapezoidal or triangular mucoperiosteal flap is formed, which is carefully prepared with a small raspator or freer, depending on the size and case of the bone.

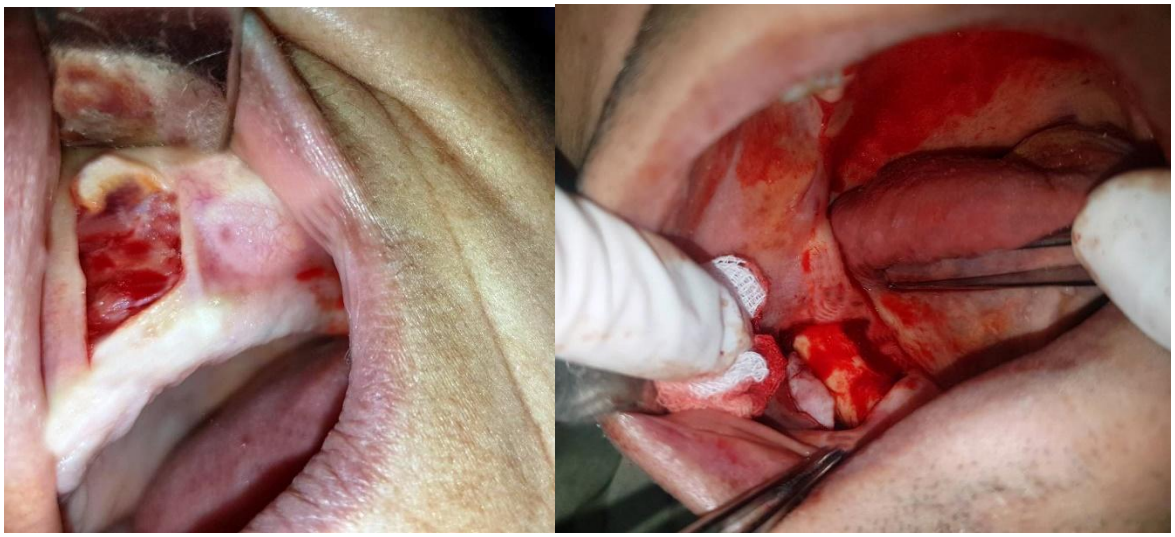


A **B**

C **D**



E **F**



G **H**

I **J**

K

Fig.18 – mucoperiosteal flap (A,B,C,D,E,F,G,H,I,J,K)

All muscle and connective tissue attachments are cut and dissected with a scalpel, scissors, raspator or freer. The mucoperiosteal flap is grasped with anatomical forceps and the base of the periosteum is carefully cut along its entire length with a scalpel or surgical scissors. This ensures the mobility of the flap and provides an opportunity to work on the osteonecrotic lesion.

The next step in the surgical procedure is the excision of the osteonecrotic lesion. With the help of bone cutters and curettes, a sequestrectomy and removal of the granulation tissue is performed. The place is tamponade until homeostasis is achieved.

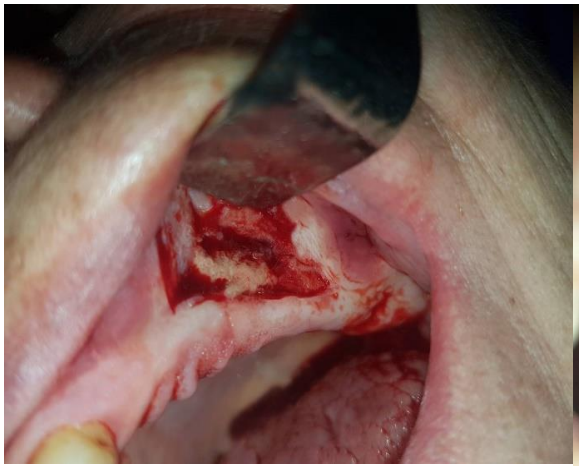
The placement of the membrane with platelet-rich fibrin - PRF is carried out after drying the area. It is positioned carefully with tweezers.

A

B

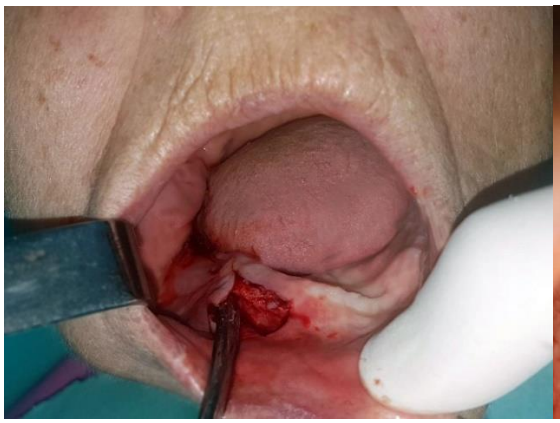
C

D

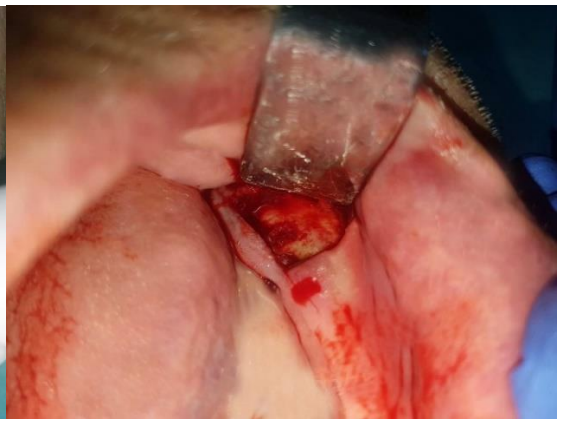


E

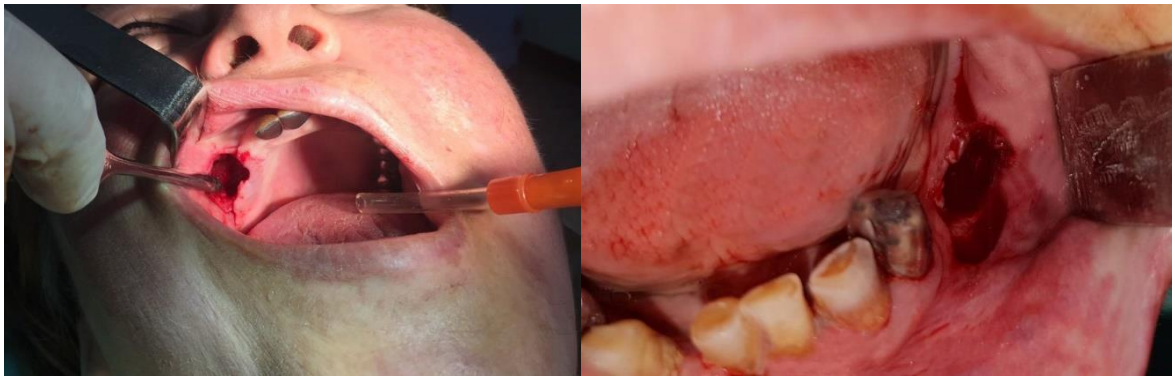
F



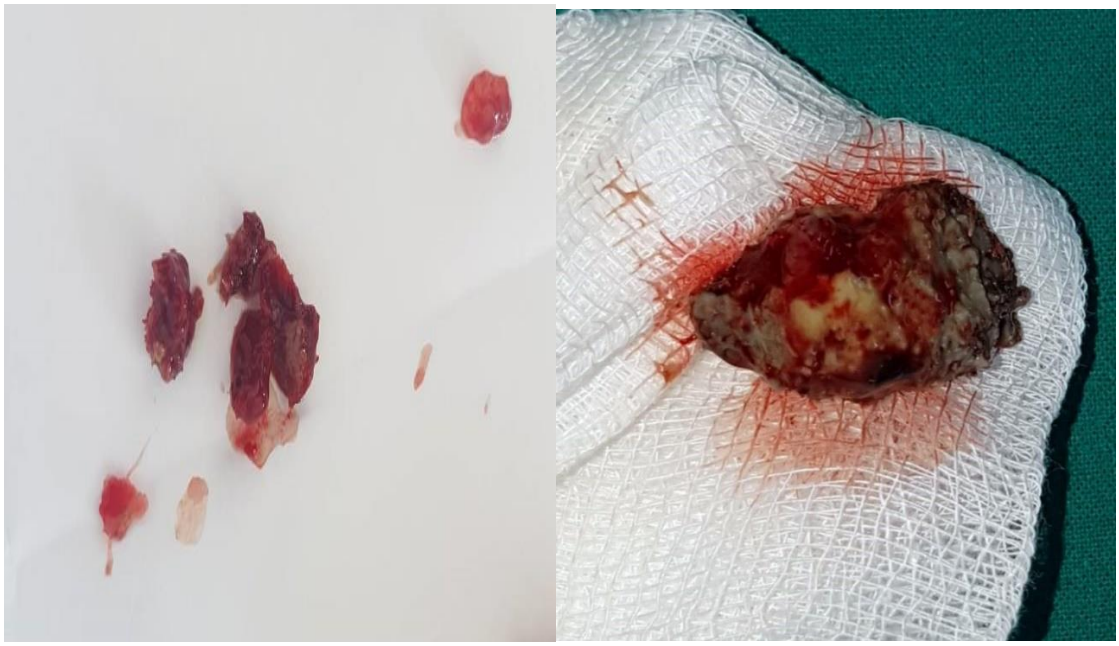
G



H



I **J**



К **L**

Fig.19. – Excision of the osteonecrotic lesion (A, B, C, D, E, F, G, H, I, J, K, L)

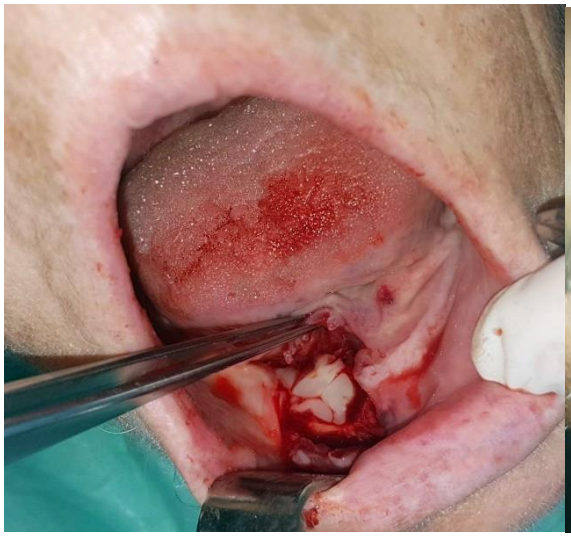
The PRF membrane is sutured using a micro needle holder and a needle ½ with atraumatic absorbable thread 000 or 0000 -

A

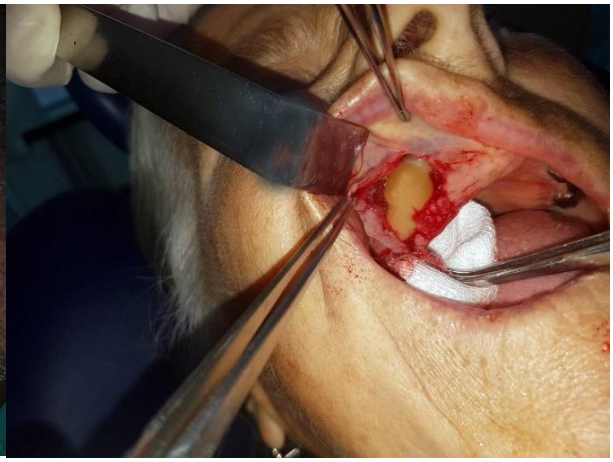
B

C

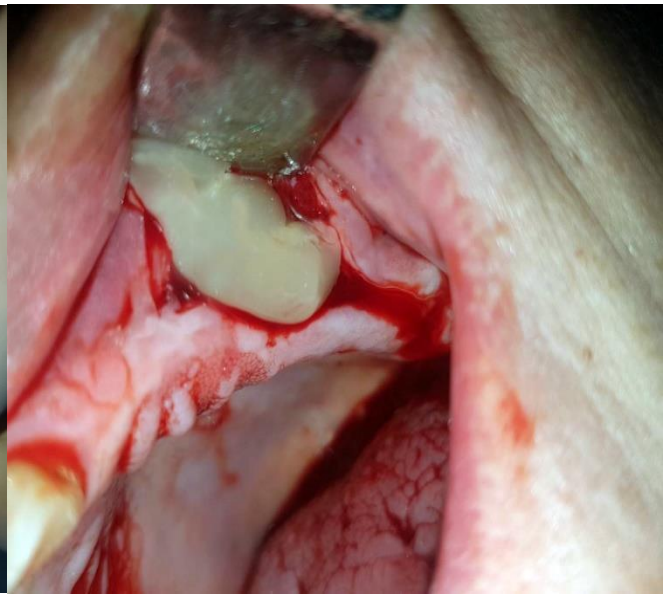
D



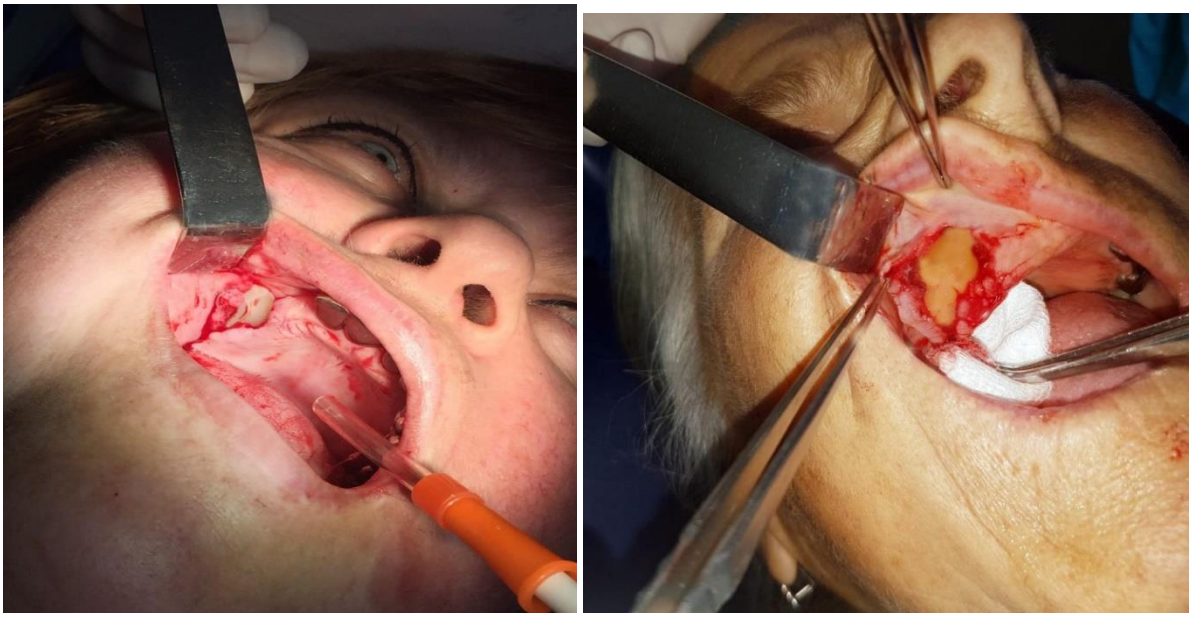
E **F**



G **H**



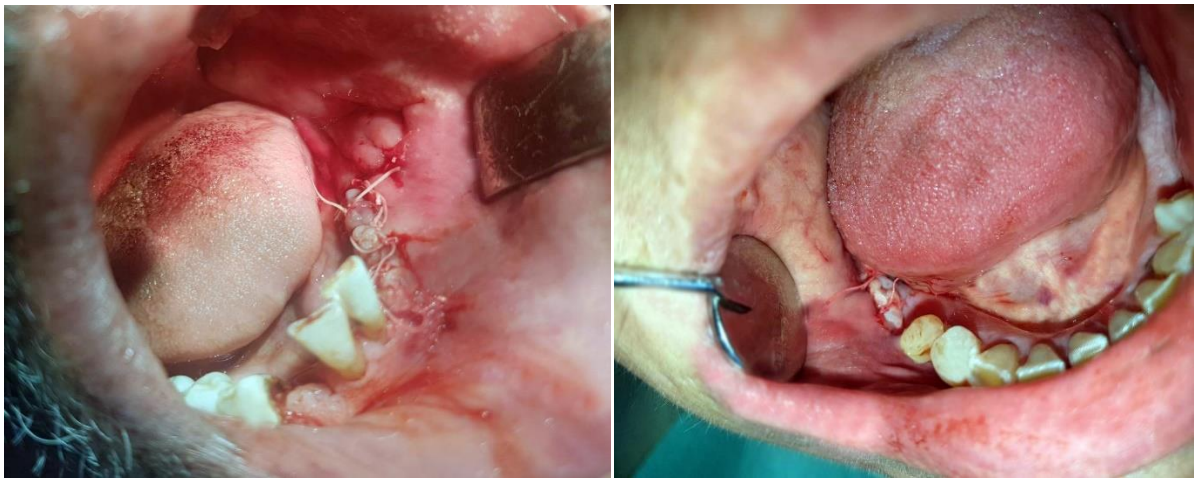
I **J**



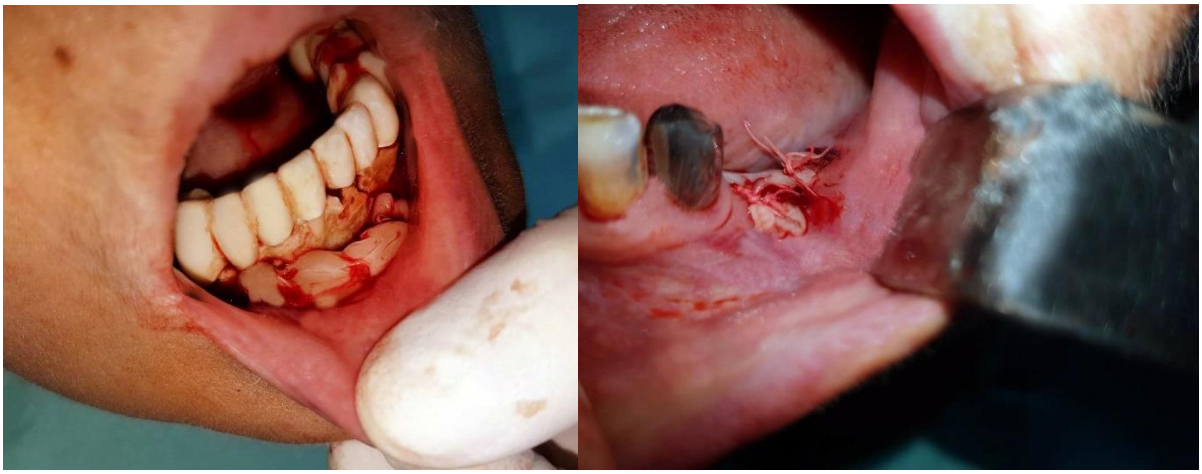
K **L**

Fig.20. The placement of the PRF membrane (A, B, C, D, E, F, G, H, I, J, K, L)

The inserted and sewn PRF membrane is covered with the mucoperiosteal flap, which is also sutured with the help of a micro needle holder and a needle ½ with absorbable thread 0000. The suturing of the PRF membrane is performed with the following technique: a vertical seam is done by means of which the tops of the flap are fixed.



A **B**



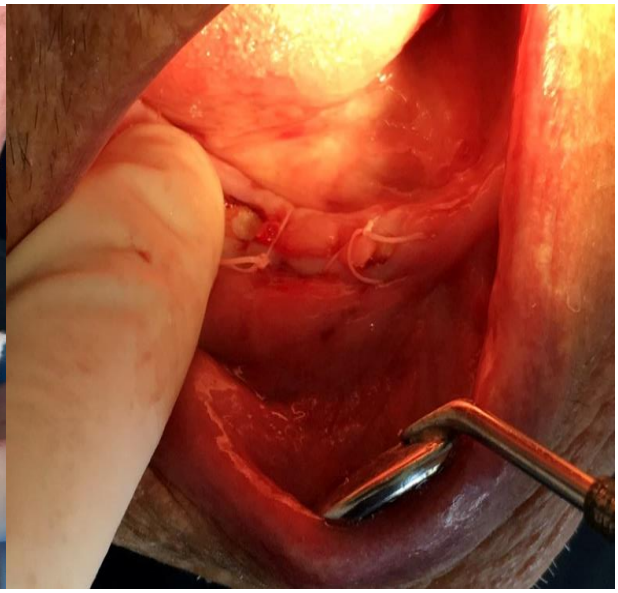
C **D**

Fig.21. Suturing of the membrane (A, B, C, D)

In the other sections, the flap is sewn with simple interrupted suture. Once all the stitches have been made, the flap is pressed with a sterile gauze for 3-5 minutes. All sutures are removed on the seventh to ninth day after surgery.

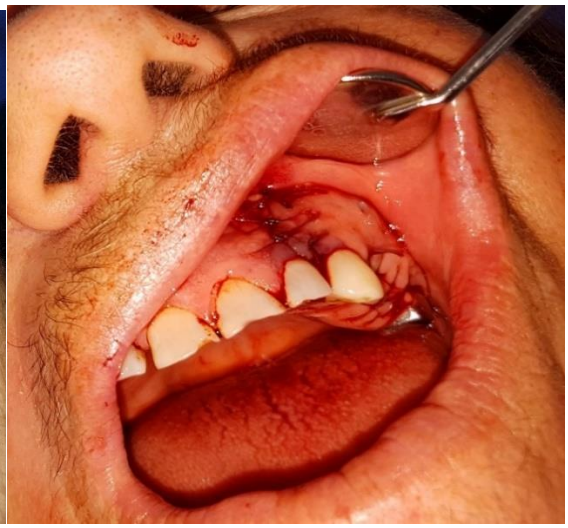
A **B**

C **D**



E **F**

G **H**



I **J**

K **L**

Fig. 22. Final sutures (A, B, C, D, E, F, G, H, I, J, K, L)

2.2.4.3. Technique for making the PRF membrane

Platelet-rich fibrin is prepared immediately before surgery. The PRF membrane (PRFm) is made with Choukroun technique after drying the blood clot from platelet-rich fibrin, obtained after the patient's blood is centrifuged. The sequence of the technology is as follows: The skin of the hand (left or right, depending on the permeability of the vessels after chemotherapy) of the forearm is cleaned with a soaked in disinfectant tampon, followed by venipuncture. Using needle device №20, connected to a 10-ml sterile anticoagulant-free syringe, 10 ml of blood is taken and stored in specially designed 10-ml glass tubes. Depending on the case, more than two blood tubes might be taken from the patient. Other substances must not be placed or mixed in the blood. Immediately after collection, the blood is placed in a laboratory centrifuge, the one used here is EBA 200 of Hettich Zentrifugen (Andreas Hettich GmbH & Co. KG, Germany).

A **B**

C **D**

E

Fig. 23. Laboratory centrifuge EBA 200 of Hettich Zentrifugen (Andreas Hettich GmbH & Co. KG, Germany) (A, B, C, D, E)

Fig. 24. Blood collection

The 10-ml blood from the tube is centrifuged for 12 minutes at 2600 rpm. Then a fibrin clot is formed, which is called Advanced - PRF (Choukroun's A-PRF ™). Advanced - PRF is an improved formula of ordinary PRF clot, with increased platelet concentration and increased leukocyte content in the fibrin clot.

Fig.25. PRF in a test tube

The fibrin clots are removed from the tube with long straight anatomical forceps. Using scissors or a scalpel, the platelet-rich fibrin clot is separated from the red blood cells (erythrocytes), then dried and spread into a PRF membrane.

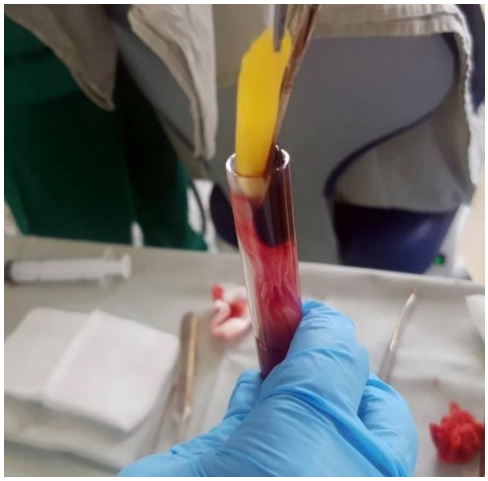
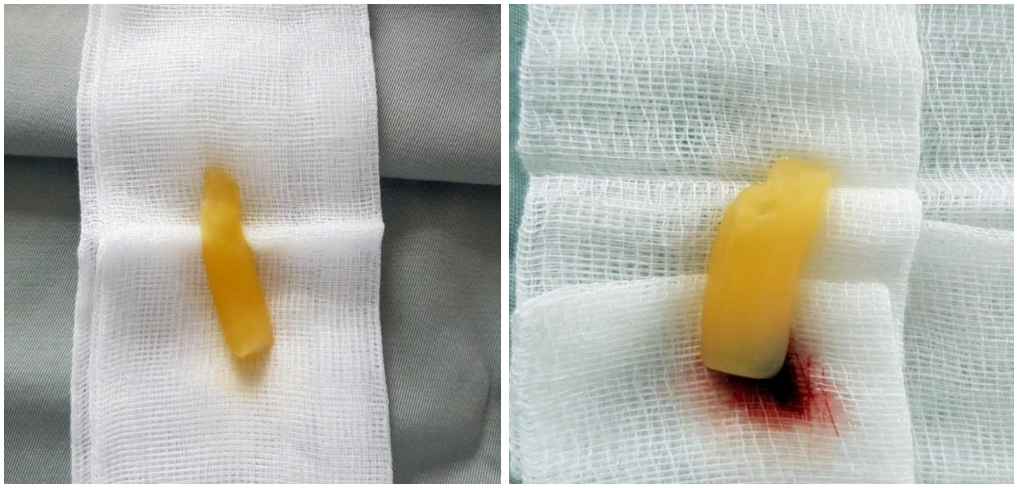


Fig.26. Removing the PRF from the tube



A **B**

C **D**

Fig. 27. PRF membrane (A, B, C, D)

The spread depends on the size of the flap, as the size of the PRF membrane must be covered. After sizing and covering of the flap with the PRF membrane, it is sewn in place with absorbable suturing material.

2.2.4.4. Postoperative care of the group with PRF treatment

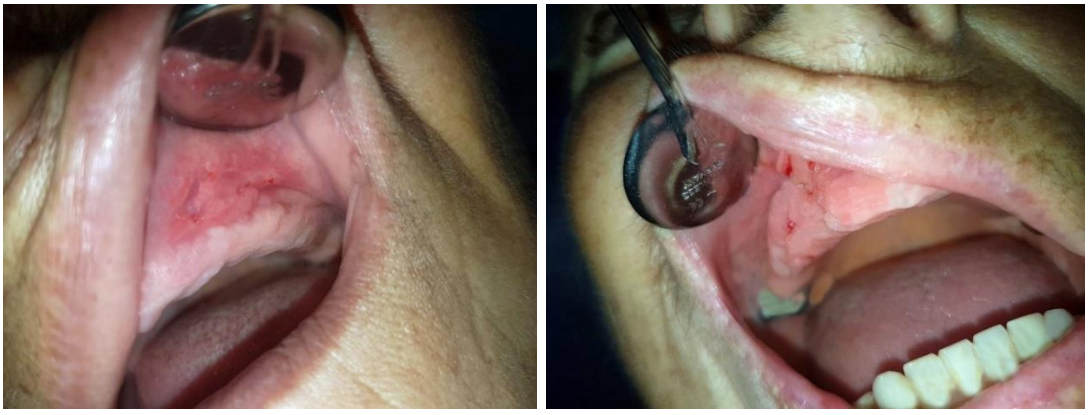
After surgery, patients were prescribed a 3-day-long non-steroidal anti-inflammatory therapy (Nimesulide 2 x 100 mg) and one-minute-long mouth rinses three times a day for 14 days with 0.12% chlorhexidine solution.

Patients were instructed to apply cold compresses in the area of the operation during the first two days after the intervention, as well as to rest the head on a high pillow during sleep and rest time. We also recommended a nutrition plan, which consists of fluid and porridge intake in the first week after surgery.

We performed the first follow-up examination on the first day after the operation, when the patients were still in the clinic. Upon leaving we gave each one of them instructions for oral hygiene for the first seven days and thereafter. During the first days, they had to treat the surgical site carefully, cleaning it only with swabs soaked in antiseptic solution. Afterwards, patients were recommended to brush their teeth thoroughly at least twice a day with a soft brush and a low-abrasive toothpaste. We demonstrated the movements that should be performed to achieve a greater effect when brushing teeth. We discussed as well bad habits and the wrong movements with the brush in the process of teeth cleaning.

We performed follow-up control examinations:

- on the 7th day, when the sutures were removed;



A **B**

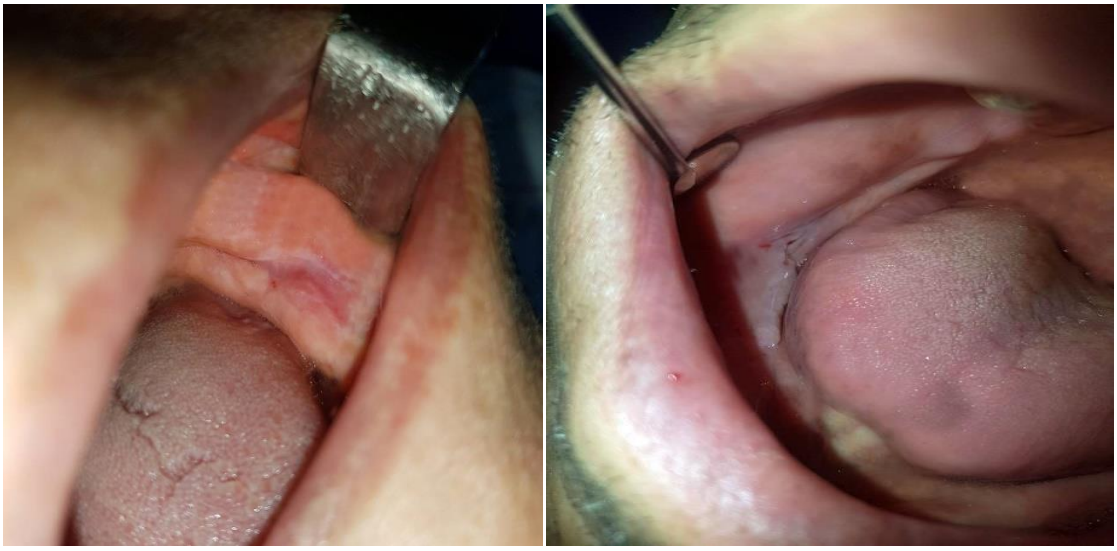
C **D**

E

Fig.28. Follow-up control examination on the 7th day (A, B, C, D, E)

- on the 14th day for swelling, redness, healthy granulation tissue and signs of epithelialization;

A **B**



C **D**

Fig.29. Follow-up control examination on the 14th day (A, B, C, D)

- on the 30th day for swelling, redness, healthy granulation tissue and signs of epithelialization;

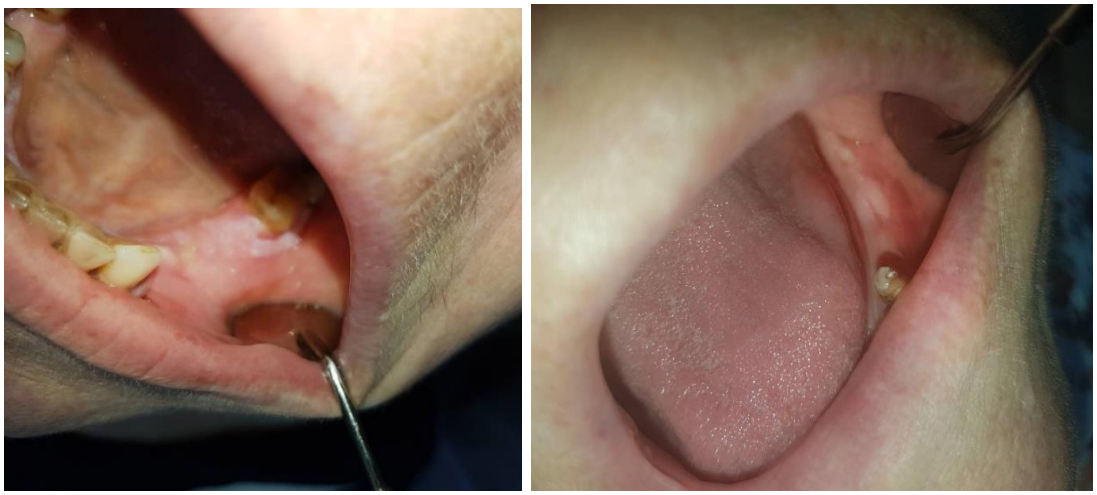
A **B**


C **D**

- on the 90th day for swelling, redness, healthy granulation tissue and signs of epithelialization;


A **B**


C **D**



E **F**

G **H**

I

Fig.30. Follow-up control examination on the 90th day (A, B, C, D, E, F, G, H, I)

- on the 6th month we performed computed tomography.

2.2.3. Statistical methods

The statistical methods used for data analysis are in accordance with the research tasks and the type of measuring scales. [5, 98] Continuous values are presented as average and standard deviation. An independent samples t-test is used to statically compare two separate groups of patients or two types of treatments. For intragroup tracking of the values of a certain quantity, a paired samples t-test was used for related samples.

Frequency measurements are summarized in number and percentages. The Chi-square test was used for statistical comparison of proportions for larger samples, and the Fisher's test was used for smaller samples.

Statistical significance was reported at an acceptable error level alpha (alpha) = 5% ($p < 0.05$), but in the description of the results in the next chapter the results can be presented, where it is most significant, at an error level ≤ 1% ($p \leq 0.01$)

The results are summarized in tables and figures. The data analysis was done with the statistical programs IBM SPSS, version 25 (2017), Minitab 18 (2017). The specific statistical methods for the individual sectors / tasks are as follows:

Statistical methods describing the patients treated in the clinic. Much of the data in this sector is presented in numbers and percentages and compared using the Chi-square test. Age is summarized in averages and age range. Age comparison between the sexes was made with independent samples-t-test.

Statistical methods for Task 1.

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.

Statistical methods for Task 2.

The peculiarities of the radiological symptoms in drug-induced osteonecrosis of the jaws are presented in number and percentage. Fisher's test was used to statistically compare the proportions between the two treatments, PRF and conservative, and separately for each treatment.

Statistical methods for Task 3.

This task provides a comparative radiological evaluation of the results of treatment of drug-induced bone necrosis of the jaws, conservatively (medically) and surgically using PRF. Results are presented as average and standard deviation. The statistical comparison of the two groups of patients at different times was made with independent-samples t-test. Intragroup

development in the average values of the parameters was monitored over time with t-test for dependent samples.

Statistical methods for Task 4.

In the second task, clinical indicators are monitored in both groups of patients, those treated surgically with PRF and those treated conservatively, at five points in time: immediately after the intervention; on the 7th, 14th, 30th and 90th day after the intervention. The results are presented in numbers and percentages for both groups of patients. The proportions between the two groups were compared using the Fisher's test for each time point: immediately after the intervention, on the 7th, 14th, 30th and 90th day after the intervention. The Fisher test was also used to track the change in the percentage of a particular clinical indicator in each group.

III. RESULTS FROM PERSONAL RESEARCH

1.Results on the first task

For the purpose of this task, the following analyzes were performed:

1. The percentage change in the frequency of MRONJ from 2015 to 2018 has been calculated, and the number from 2015 has been used as a starting point for the calculation.

2. The percentage distribution of MRONJ to the used drugs is presented: Alendronic acid, Ibandronic acid and Risedronate sodium and a statistical comparison of the percentage distribution of MRONJ by years (2015, 2016, 2017, 2018) is made using the Chi-square test to determine the drug, which has a statistically significant association with the presence of MRONJ.

Change in the frequency of MRONJ from 2015 to 2018

The frequency of MRONJ in the period 2015-2018 is presented in Figure 36. There is a gradual increase in the period 2015-2017 and a slight decline in 2018, but the reason for this is that the data for 2018 are only for the first six months. If the trend continues at this rate until the end of the year, the increase in the number of cases could almost double compared to previous years.

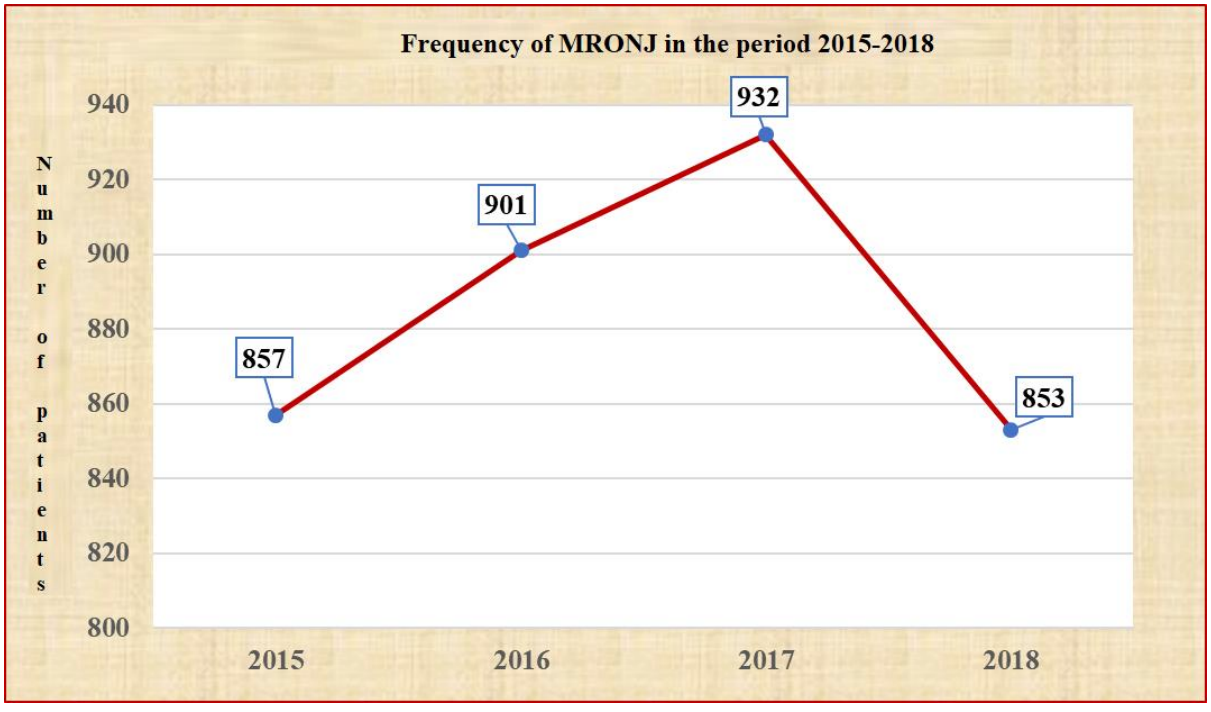


Fig 31. Frequency of MRONJ in the period 2015-2018

The percentage change in the frequency of MRONJ is illustrated in Figure 37. Between 2016 and 2015, an increase of 5.15% is observed. Between 2017-2015, the increase is 8.75%,

while between 2018 and 2015 there is a decrease of 0.47%, which is due to the fact that the data are only for the first half of the year.

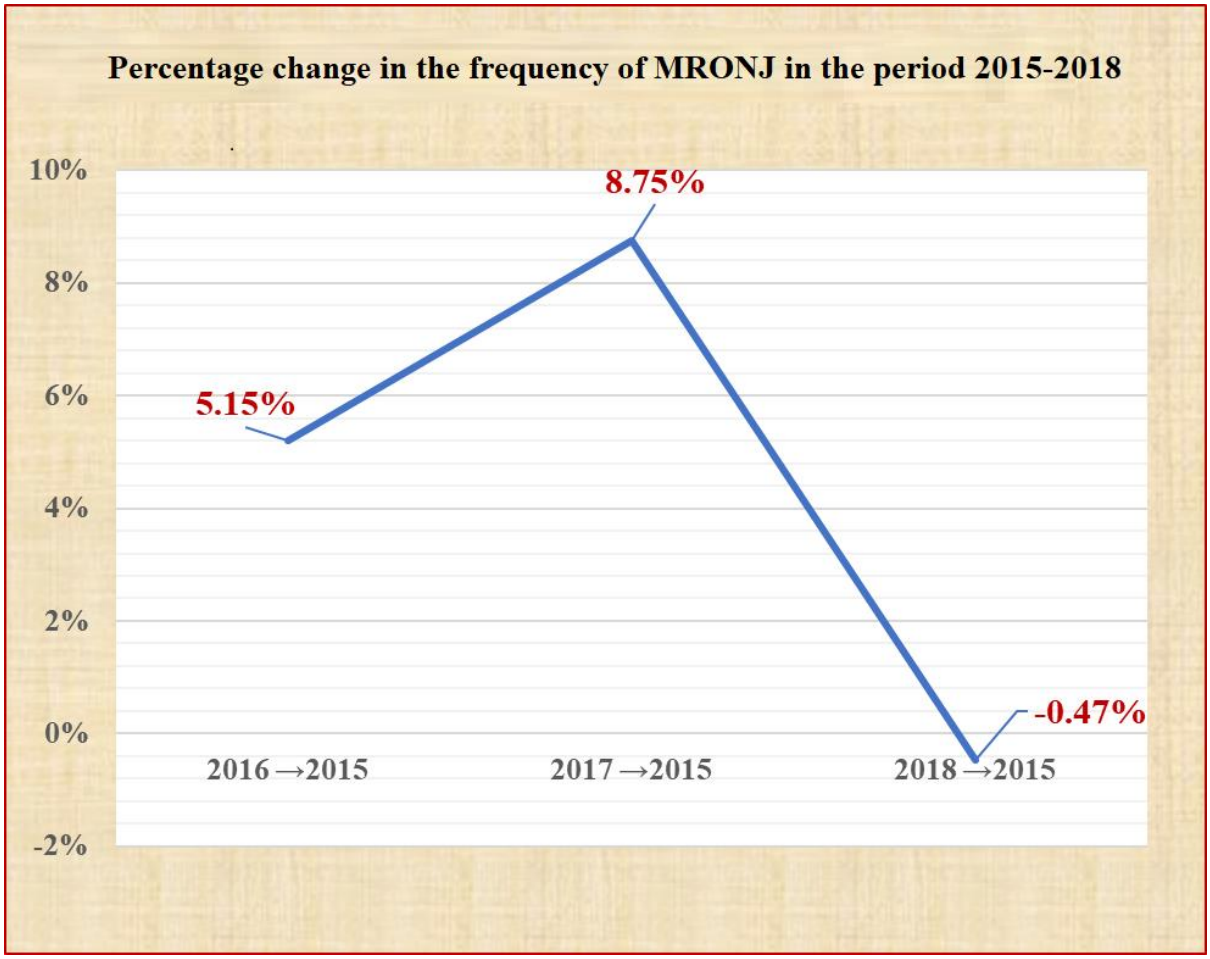


Fig. 32. Percentage change in the frequency of MRONJ in the period 2015-2018

The percentage distribution of MRONJ in relation to the used drugs and statistical comparison of the percentage distribution.

In 2015, out of a total of 857 patients with MRONJ, 1% (N = 9) were treated with alendronic acid, 96% (N = 825) with ibandronic acid and 3% (N = 26) with risedronate sodium.

Patients with MRONJ treated with ibandronic acid account for a significantly higher percentage of those treated with the other two drugs compared to the statistical, $p < 0.001$.

In 2016, out of a total of 901 patients with MRONJ, 5% (N = 49) were treated with alendronic acid, 95% (N = 855) with ibandronic acid and no patients were treated with risedronate sodium. The percentage of patients with MRONJ treated with ibandronic acid was significantly higher than these treated with alendronic acid, $p < 0.001$.

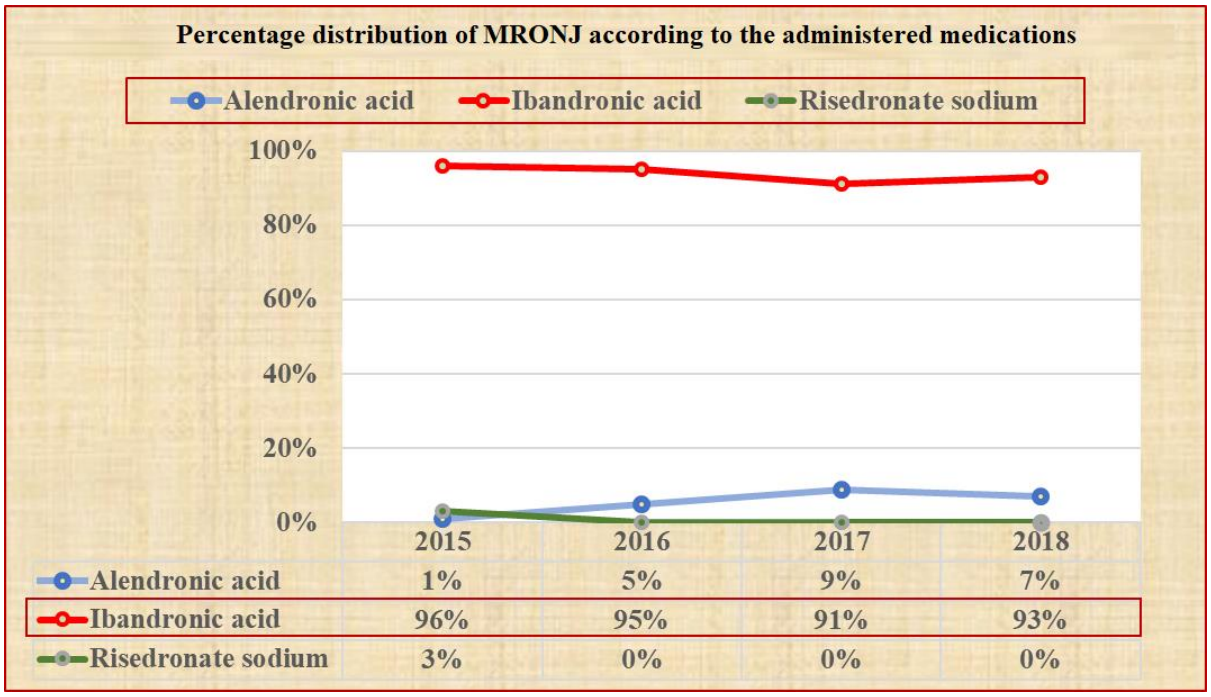
In 2017, the trend is very similar. Out of a total of 932 patients with MRONJ, 9% (N = 81) were treated with alendronic acid and 91% (N = 854) with ibandronic acid.

There are no patients treated with risedronate sodium. The percentage of patients treated with ibandronic acid is significantly higher than that of those treated with alendronic acid, p <0.001.

In 2018, there is a percentage distribution similar to the previous ones. Of a total of 853 patients with MRONJ, 7% (N = 63) were treated with alendronic acid, 93% (N = 790) with ibandronic acid, and no patients were treated with risedronate sodium.

Patients treated with ibandronic acid account for a significantly higher percentage than those treated with alendronic acid, p <0.001

In summary, there is a strong trend of a statistically significant association between ibandronic acid treatment and the presence of MRONJ.



	2015	2016	2017	2018
Alendronic acid	1%	5%	9%	7%
Ibandronic acid	96%	95%	91%	93%
Risedronate sodium	3%	0%	0%	0%

Fig. 33. Percentage distribution of MRONJ according to the administered medications

Summary of the first task

1) The frequency of MRONJ in the period 2015-2018 is highest in 2015-2017, with a slight decrease in 2018, which, however, is due to the fact that the data used are only for the first half of the year. Their hypothetical doubling shows a much higher frequency compared to previous years.

2) There is a strong trend of statistical significance of the treatment of MRONJ with ibandronic acid.

2. Results on the second task

In the period 2013-2017, a total of 750 patients passed through the clinic of maxillofacial surgery "St. George", of which 237 people were treated. 55% of them are women and 45% are men. There were 148 patients, whose lower jaw was treated, 52% women and 48% men. 89 patients were treated in the upper jaw, of which 54% were women and 46% were men.

The age of the patients is between 41 and 85 years (mean age 68.8 years). All patients were diagnosed with medication-related osteonecrosis of the jaw caused by bisphosphonate treatment.

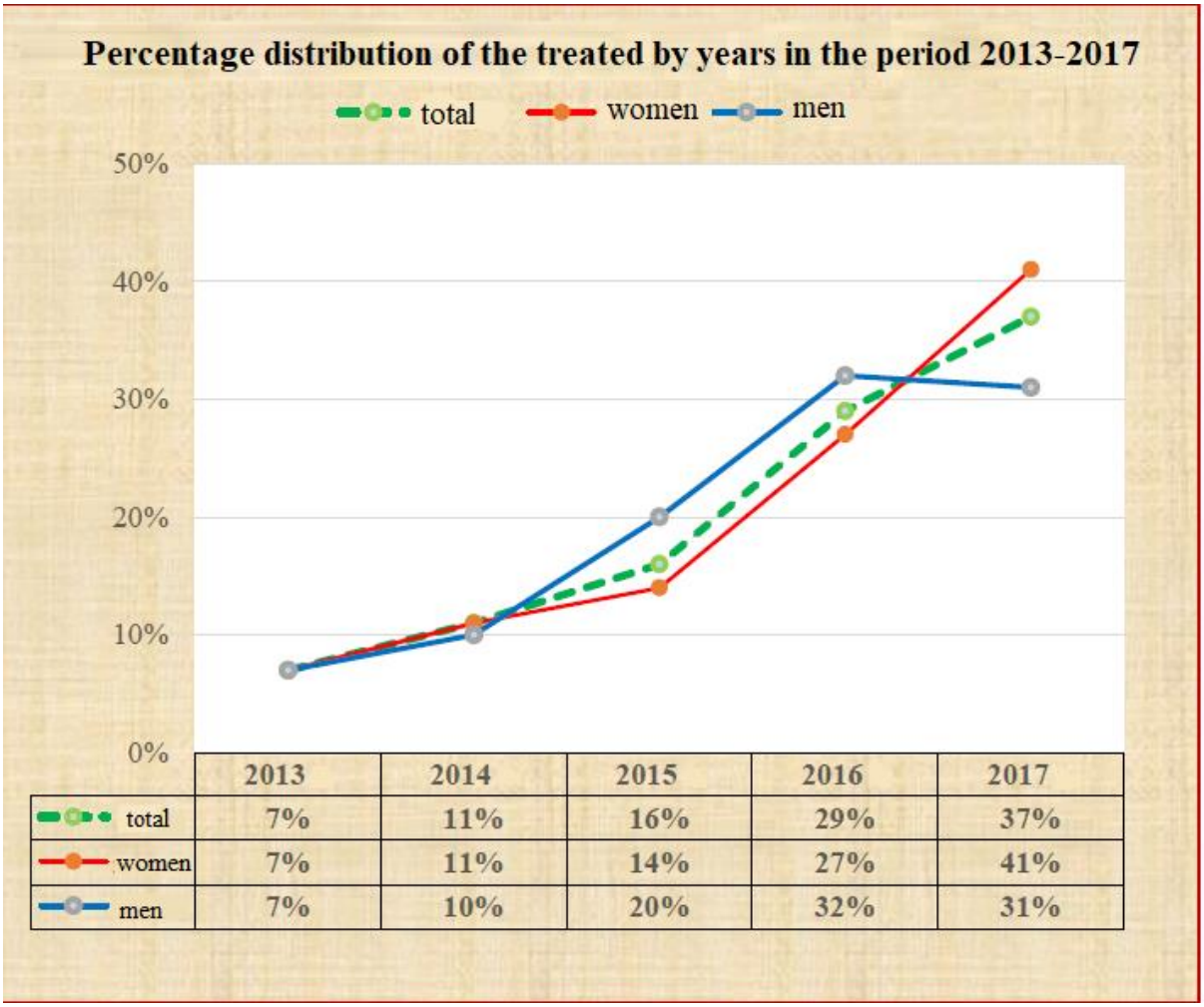
The distribution of the treated patients by years is presented in Table 2. In the period 2013-2017 there is a gradual increase in the total number and the number of women treated there.

Table 2. Treated in the period 2013-2017

	2013	**2014**	**2015**	**2016**	**2017**
Total	**19**	**30**	**46**	**82**	**105**
Women	12	20	25	48	72
Men	7	10	21	34	33
Lower jaw	**10**	**22**	**38**	**65**	**74**
Women	5	17	23	47	61
Men	5	5	15	18	13
Upper jaw	**9**	**8**	**8**	**17**	**31**
Women	7	3	5	9	19
Men	2	5	3	8	12

The highest number of treated patients was observed in 2017 as a whole and separately for both jaws. The only exception to this trend is noted in men in the lower jaw, where there is a slight decrease in the number of patients in 2017.

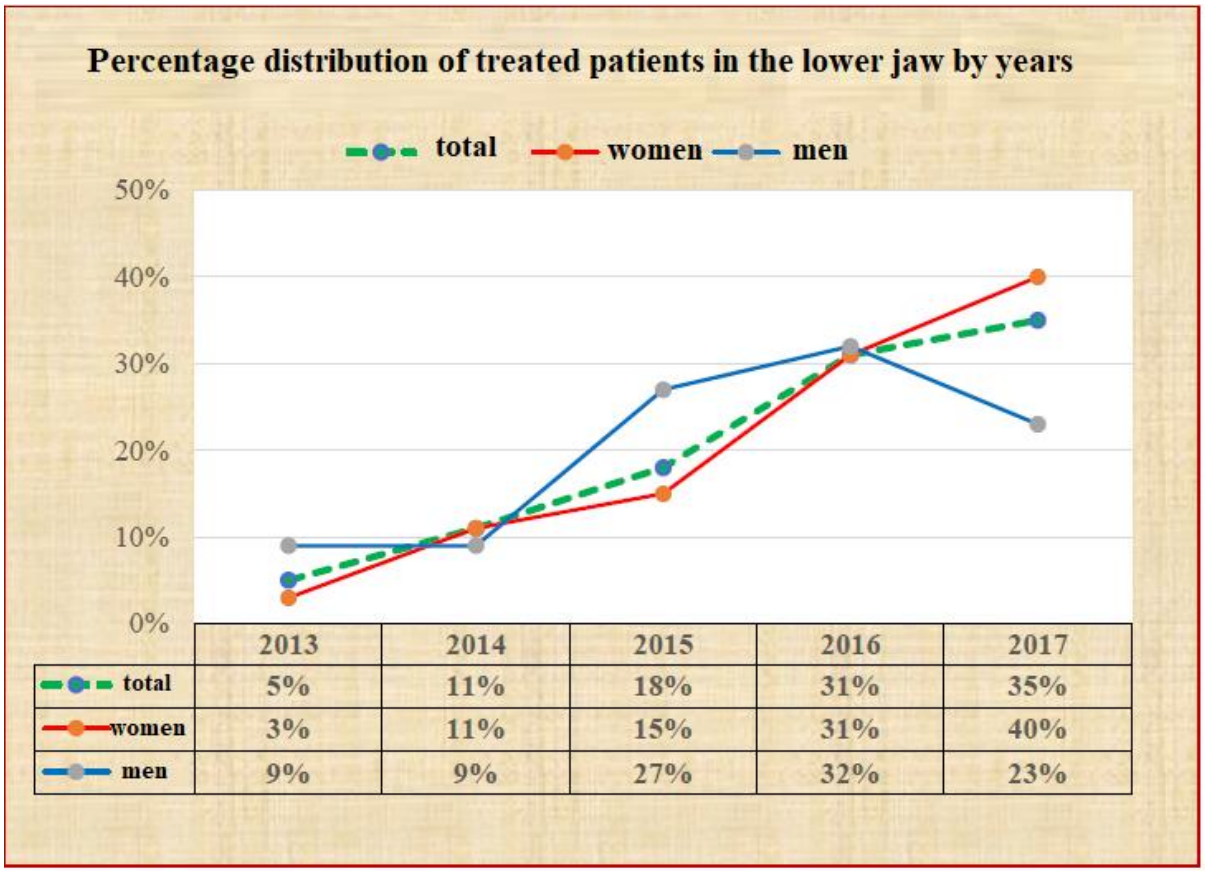
The percentage distribution of the treated in the clinic by years is presented in Figure 34. In the period 2013-2017 there is a gradual increase in the total percentage and that of women.



	2013	2014	2015	2016	2017
total	7%	11%	16%	29%	37%
women	7%	11%	14%	27%	41%
men	7%	10%	20%	32%	31%

Fig. 34. Percentage distribution of the treated by years in the period 2013-2017

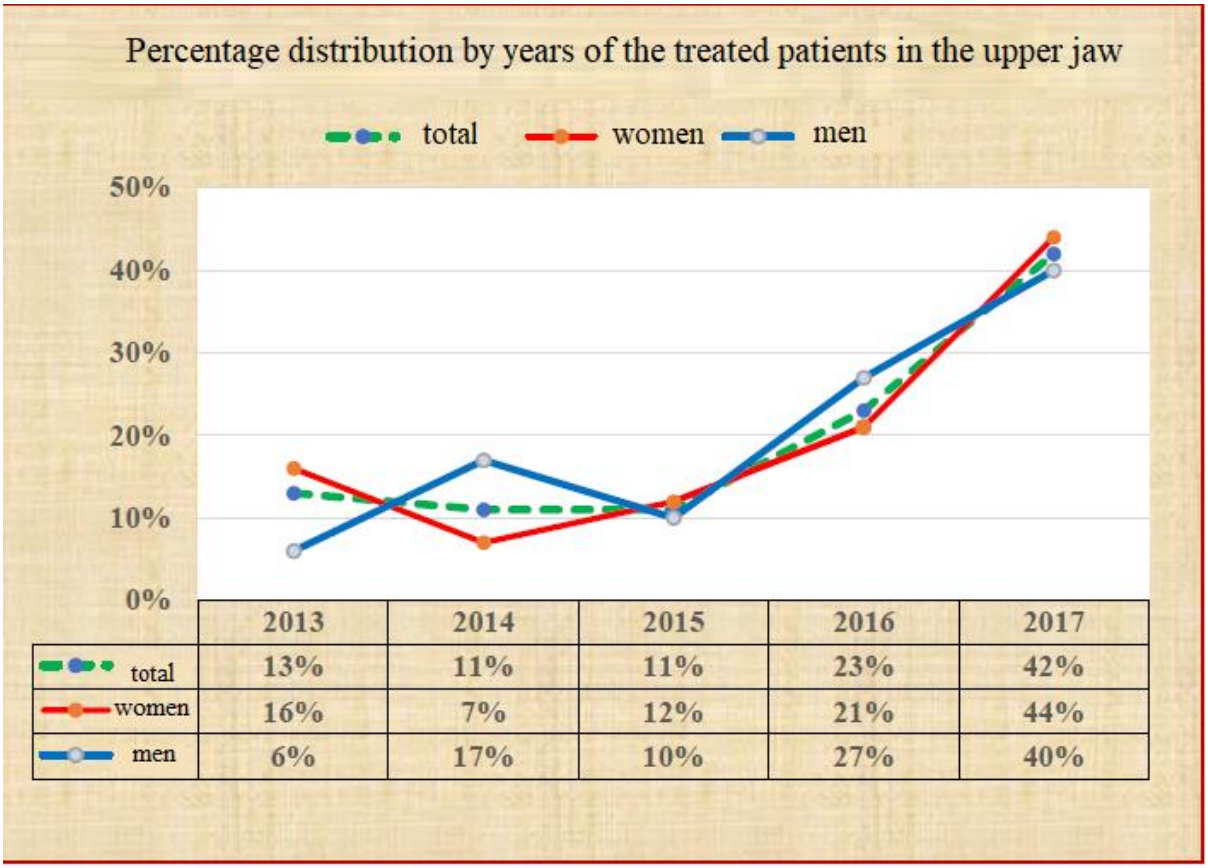
Figure 35 shows the percentage distribution of MRONJ localization in the lower jaw by years. There is a gradual increase in the number of women treated in the lower jaw, with the highest percentage reported in 2017. This increase also affects the overall percentage, which is also higher. No increase was observed for men, between 2013 and 2014. There is such an increase between 2014 and 2016, and between 2016 and 2017 a decrease of 9%.



	2013	2014	2015	2016	2017
total	5%	11%	18%	31%	35%
women	3%	11%	15%	31%	40%
men	9%	9%	27%	32%	23%

Fig. 35. Percentage distribution of treated patients in the lower jaw by years

The percentage distribution of MRONJ localization in the upper jaw by years is illustrated in Fig. 36. Overall, between 2013 and 2015 there was a decrease of 2%; in 2016 there is an increase from 11% to 23%; in 2017 the highest relative share of 43% was reported. The percentage decreased from 16% in 2013 to 7% in 2014 for women, then increased to 12% in 2015. A new increase followed in 2016 and in 2017 the percentage reached 44%. For men, between 2013 and 2014 there was an increase from 6% to 17%; in 2015 the percentage decreased to 10%; followed by an increase in 2016, with the highest rate again reported in 2017.



	2013	2014	2015	2016	2017
total	13%	11%	11%	23%	42%
women	16%	7%	12%	21%	44%
men	6%	17%	10%	27%	40%

Fig. 36. Percentage distribution by years of the treated patients in the upper jaw

Distribution of treated patients according to the type of treatment

The patients were divided into two groups according to the method of their treatment, and the results were monitored until the sixth month after the intervention. The first group was treated with **conservative (medication) treatment**, and the second group was treated with surgical treatment with **platelet-rich fibrin (PRF).**

The distribution in the two groups is as follows (Fig. 37):

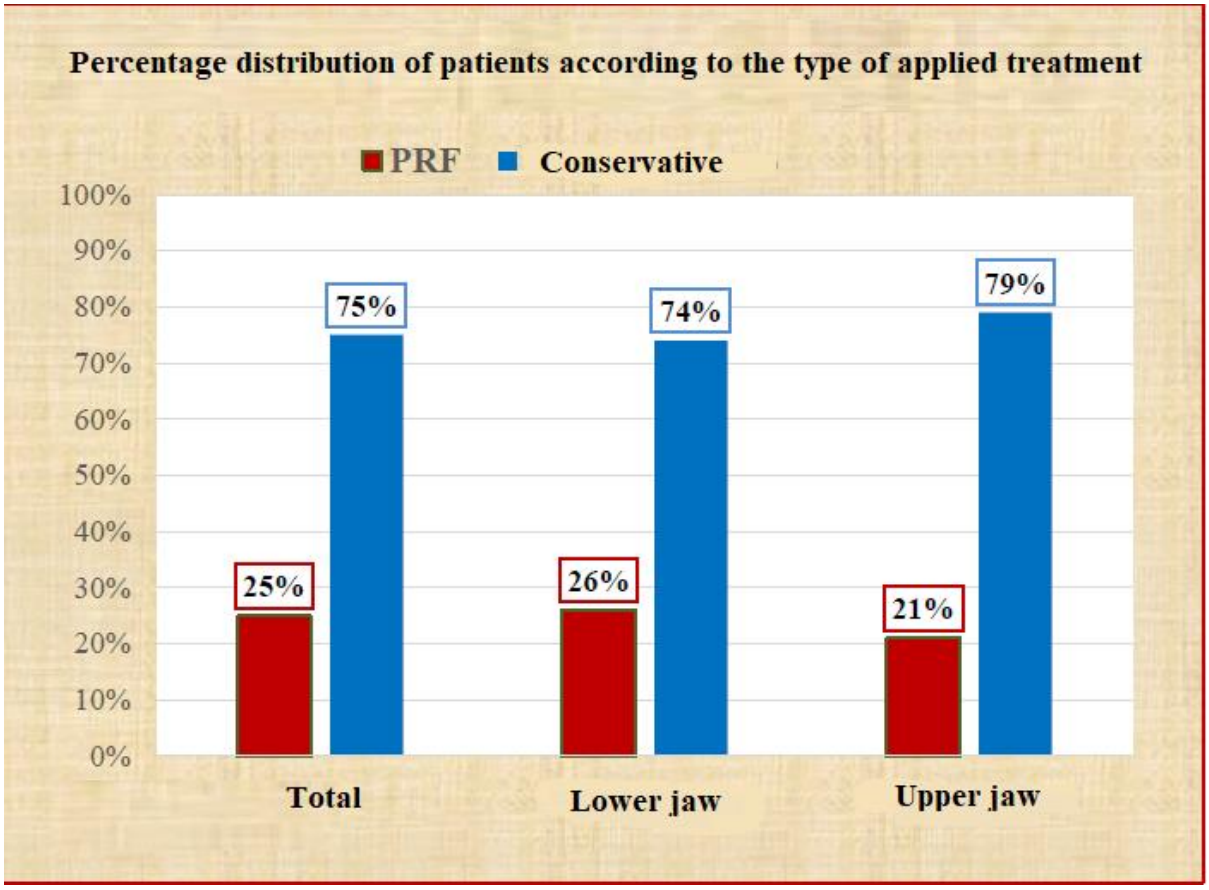


Fig. 37. Percentage distribution of patients according to the type of applied treatment

It can be seen that conservative treatment is applied in the majority of patients: the overall treatment rate is 75%, 74% in the lower jaw; 79% in the upper jaw. Patients treated with PRF accounted for a lower percentage, a total of 25%, a lower jaw 26%, an upper jaw 21%.

Treatment with platelet-rich fibrin was performed on 59 teeth, of which 38 in the lower jaw (21 teeth on the left and 17 on the right) and 21 in the upper jaw (10 teeth on the left and 11 on the right). Conservative (**medication**) treatment was applied to 178 teeth, of which 110 in the lower jaw (58 teeth on the left and 52 on the right) and 80 in the upper jaw (42 teeth on the left and 38 on the right). The first group was treated with a membrane of platelet-rich fibrin (PRFm) and the second group with intravenous antibiotic treatment.

Table 3: Distribution of the groups in the study by method of treatment and localization of MRONJ

	PRF	**Conservative (medicated)**
Total treated	**59**	**178**
Lower jaw	**38**	**110**

- left	21	58
- right	17	52
Upper jaw	**21**	**80**
- left	10	42
- right	11	38

The percentage distribution according to the type of treatment in the lower and upper jaw on the left and right is similar to that in the whole sample. Figure 38 shows that the percentage of patients undergoing conservative treatment was 73% in the lower jaw on the left, 75% in the lower jaw on the right, 81% in the upper jaw on the left and 77% in the upper jaw on the right. Treatment with PRF was performed in 27% in the lower jaw on the left, in the lower jaw on the right the percentage was 25, in the upper jaw on the left -19%, and in the upper jaw on the right -23%.

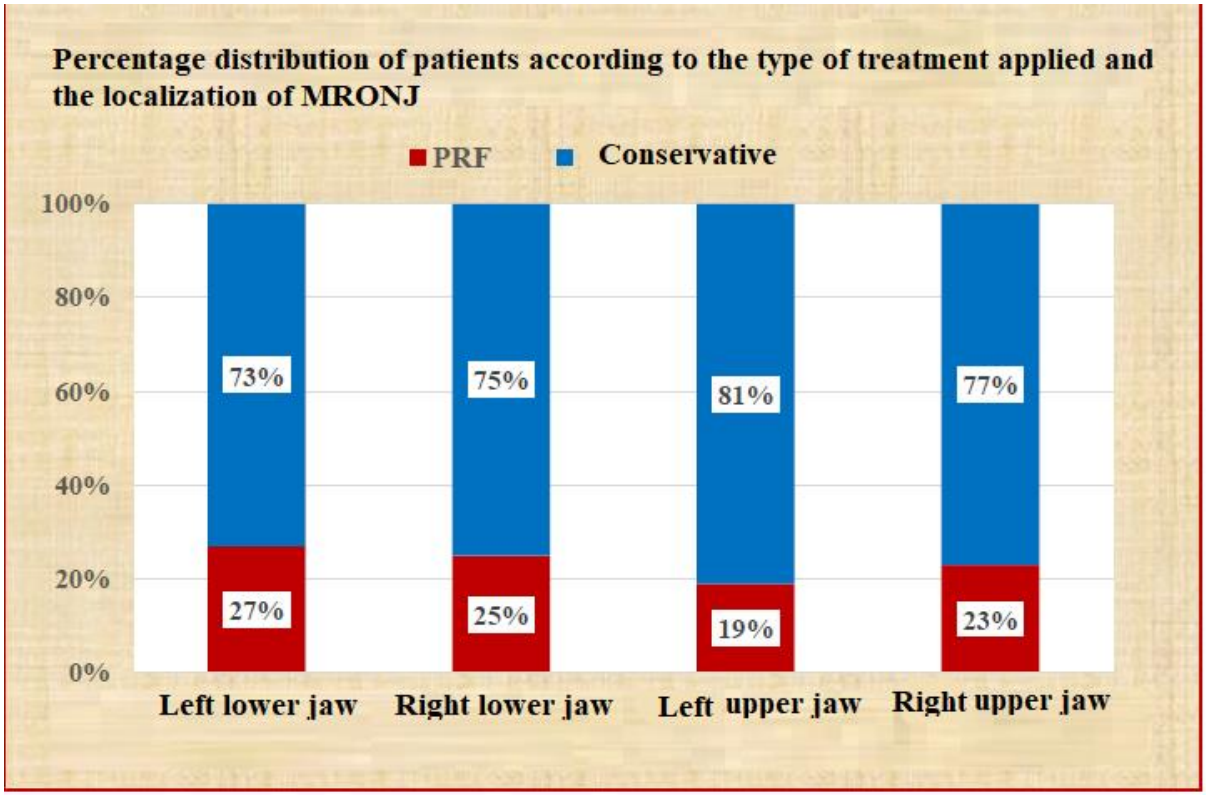


Fig. 38. Percentage distribution of patients according to the type of treatment applied and the localization of MRONJ

Data on patients treated with the PRF protocol

59 patients with a mean age of 69 years were treated with the PRF protocol. The age range of patients is between 41-87 years, with 56% of them women and 44% men. The average age for men is 71.71 years, range 50-87 years.

The average age of women is 66.54 years, with an age range of 41-83 years.

The average age of men treated with PRF was significantly higher than that of women who underwent the same treatment.

The patients who underwent treatment in the lower jaw were 38 patients, of whom 55% women and 45% men.

Treated on the left side of the jaws accounted for 55%; the remaining 45% were treated on the right. 21 patients were treated in the upper jaw, of which 57% were women and 43% were men. Patients treated on the left side of the jaws were 48% and those on the right 52%.

Table 4: Distribution of patients treated with the PRF protocol

Distribution	Total	women	men
Total	**59**	**33 (56%)**	**26 (44%)**
Lower jaw	**38 (64%)**	**21 (55%)**	**17 45%)**
left	21 (55%)	14 (66%)	7 (33%)
right	17(45%)	7 (41%)	10 (59%)
Upper jaw	**21 (36%)**	**12 (57%)**	**9 (43%)**
left	10 (48%)	7 (70%)	3 (30%)
right	11 (52%)	5 (45%)	6(55%)

Summary of the main facts about the treated patients

The following facts emerge from the description in this sector:

1) Among the treated patients, the percentage of women is higher than that of men.

2) In the period between 2013-2017, the highest percentage of patients were treated in the last two years, i.e. in 2016-2017.

3) Conservative treatment was administered to the majority of patients (average 75%); PRF treatment was administered to the remaining 25%.

4) The majority of patients treated with the PRF protocol were treated in the lower jaw (64%). The remaining 36% received treatment in the upper jaw.

This sector summarizes the results regarding the ***topographical* and *anatomical localizatio****n*** of both types of treatment, size, shadow intensity, homogeneity, type of outline and presence or absence of change in the surrounding bone.

Table 4 contains the data on the *topographical* and *anatomical localization* in the two groups of patients, presented in number and percentages

The percentage of patients with lower and upper jaw problems is similar in both treatments. Of the patients with mandibular problems, 64% were treated according to the PRF

protocol and 62% with conservative treatment, p = 0.758. Of the patients with upper jaw problems, 36% were treated with PRF and 38% with conservative treatment, with no significant percentage difference, p = 0.758.

The percentage of patients with left and right mandibular problems was also similar, with no significant difference between treatments, p = 0.852. In the treatment of the upper jaw, there is a similar distribution of patients with left and right treatment in both types of treatment, p = 0.313.

Table 4: Anatomical and topographical localization in both types of treatment

	PRF treatment	Conservatively treatment (medically)	Fisher's test P
Total	59 -100%	178 -100%	-
Lower jaw	38 -64%	110 -62%	0.758
left	21 -55%	58 -53%	
right	17 -45%	*52* -47%	0.852
Upper jaw	21 -36%	68 -38%	0.758
left	10 -48%	42 -52%	0.313
right	11 -52%	38 -48%	

Size distribution

The size of the 6th month is presented in four categories: ≤ 1 mm; > 1 - 3 mm; > 3 - 5 mm; > 5 mm. The number and percentage of patients in each category for both treatments are summarized in Table 5. A proportional comparative analysis was performed using the Fisher test. In the first category, up to 1 mm in size, 32% of PRF patients and 14% of those on conservative treatment were categorized.

The difference of 18% is statistically significant, p = 0.004. In the category> 1 - 3 mm, fall 42% of patients on PRF treatment and 51% on conservative treatment. The difference between the two percentages is 9%, which is without statistical significance, p = 0.293.

The group with sizes > 3-5 mm includes 20% of patients treated with PRF and 29% of those treated with conservative treatment. The difference in percentages is 9%, which is not significant, p = 0.236. In the last category with values> 5 mm the lowest percentage of patients are classified and it is equal for both types of treatment (6%), p = 1.00.

Table 5: Size of 6 months after treatment in both groups of patients

size	Type of treatment	Fisher's test

(mm)	PRF	Conservative	difference	p
< 1 mm	19	26		
	(32%)	(14%)	18%	.004**
up to 3 mm	25	91		
	(42%)	(51%)	9%	0.293
> 3 to 5 mm	12	52		
	(20%)	(29%)	9%	0.236
> 5 mm	3	99		
	(6%)	(6%)	0%	1

*Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

A visual illustration of the percentage distribution of patients from both treatments relative to 6-month size is presented in Figure 39.

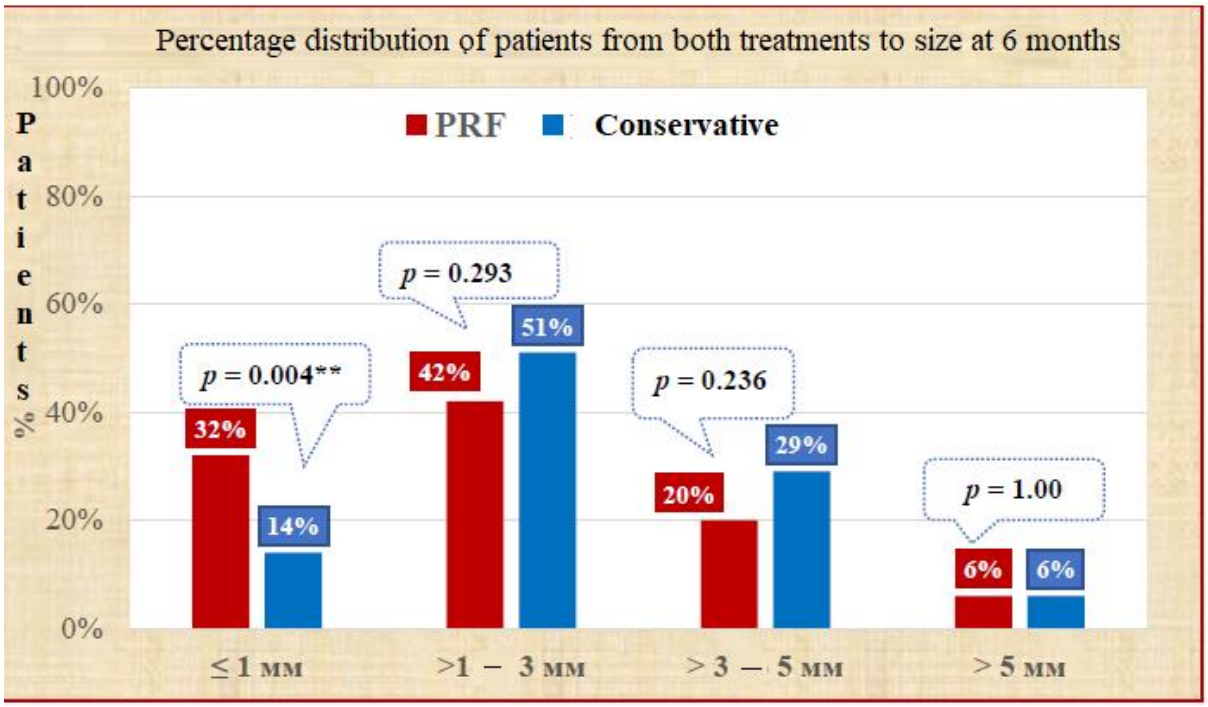


Fig. 39. Percentage distribution of patients from both treatments to size at 6 months

Separately for the PRF group, the size distribution of patients is presented in Table 6 and illustrated in Figure *40.*

Table 6: Percentage distribution of patients in the PRF group by size

PRF treatment	size (mm)			
	<1 mm	>1 -3 mm	> 3 - 5 mm	>5mm
Lower jaw	**12**	**16**	**S**	*2*
	(34%)	(46%)	(14%)	(6%)
left	8	7	3	1
	(42%)	(37%)	(16%)	(5%)
right	4	*9*	2	1
	(25%)	(56%)	(13%)	(6%)
Upper jaw	**7**	**8**	**3**	**1**

	(37%)	(42%)	(16%)	(5%)
left	4	3	1	0
	(50%)	(37.5%)	(12.5%)	0%
right	3	5	2	1
	(27%)	(46%)	(18%)	(9%)

Figure 40 shows that the majority of patients in the PRF group fall into the first two categories: ≤ 1 mm and > 1-3 mm. In general, the highest percentage is of patients with a size > 1 - 3 mm, except for the lower and upper jaw on the left, where the highest percentage is observed in the category ≤ 1 mm. The lowest percentage of patients is > 5 mm in size.

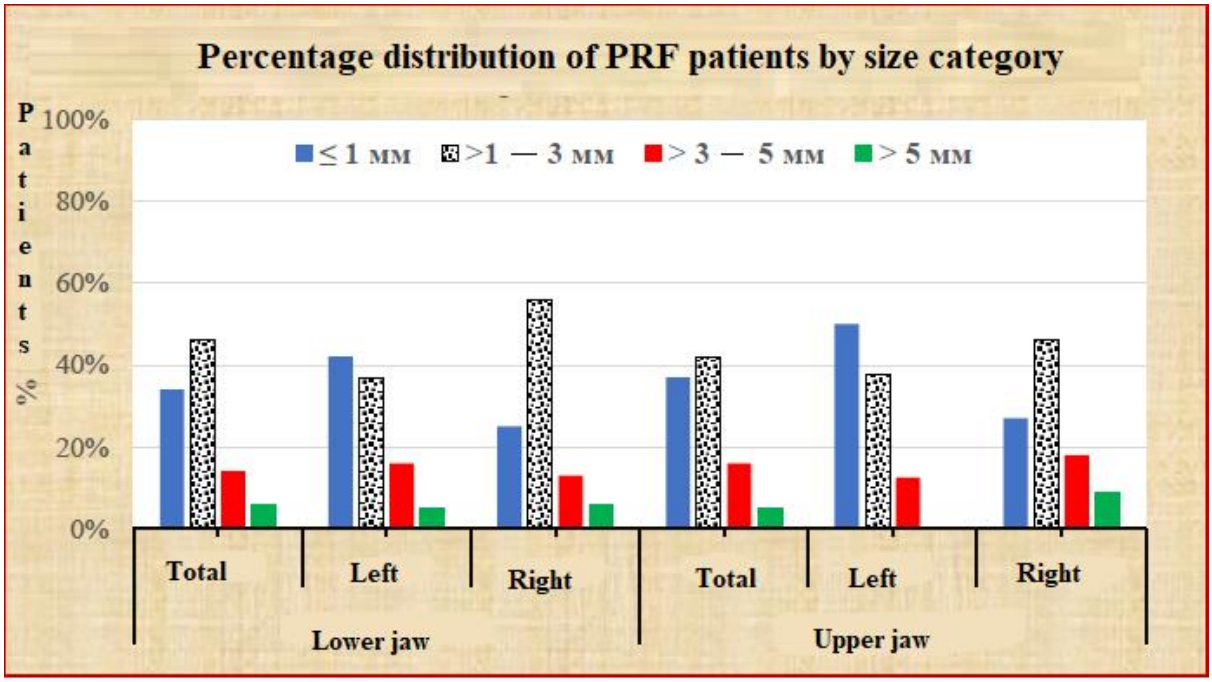


Fig. 40. Percentage distribution of PRF patients by size category

Table 7: Percentage distribution of patients on conservative treatment by size

Conservative treatment	**size (mm)**			
	<1 mm	**>1 -3 mm**	**> 3 - 5**	**>5mm**
Lower jaw	**11**	**47**	**24**	**5**
	(12%)	(54%)	(28%	(6%)
left	4	28	10	3
	(9%)	(62%)	(22%)	(7%)
right	7	19	14	*2*
	(17%)	(45%)	(33%)	(5%)
Upper jaw	15	44	28	4
	(16%)	(49%)	(31%)	(4%)
left	7	25	16	3
	(14%)	(49%)	(31%)	(6%)
right	S	19	12	0.1
	(20%)	(47.5%)	(30%)	(2.50%)

Figure 41 shows that in conservative treatment, the highest percentage of patients are > 1-3 mm in size, followed by those > 3-5 mm in size. The lowest percentage of patients is > 5 mm.

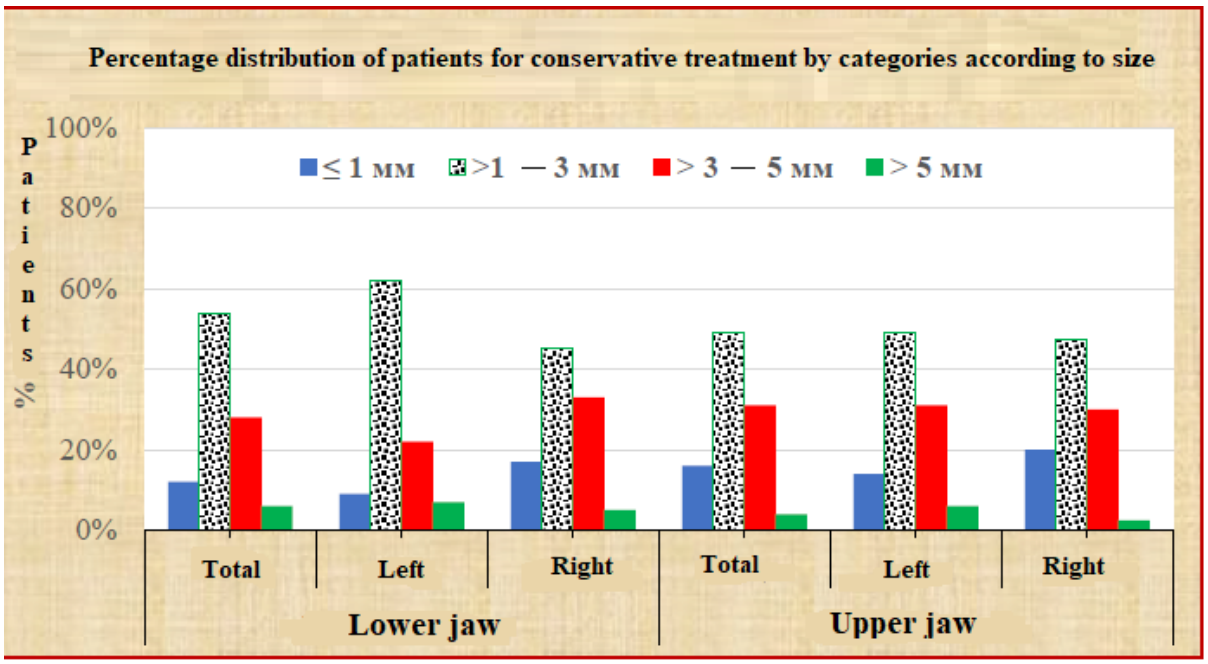


Fig. 41. Percentage distribution of patients for conservative treatment by categories according to size

Distribution according to the intensity of the shadow at 6 months after treatment

Shadow intensity was measured at 6 months after treatment. The results showed a significantly higher percentage (68%) of patients with strong shadow intensity in the PRF treatment group compared to those on conservative treatment (40%), p <0.001. In contrast, in the conservative treatment group, the percentage of patients with low intensity (60%) was significantly higher than in the PRF treatment group (22%), p <0.001. The results described above are summarized in Table 8.

Table 8: Distribution according to the intensity of the shadow in both types of treatment

Intensity of the shadow	Type of treatment		Fisher's test difference	p
	PRF	Conservative		
strong intensity	40 -68%	71 -40%	28%	.000 **
low intensity	19 -32%	107 -60%	-28%	..000

Note: *The minus sign (-) in front of the value of the difference indicates a higher percentage in the conservative treatment. * Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

The intragroup distribution as well as the intergroup distribution of patients according to the intensity of the shadow is summarized in Figure 42. In PRF treatment, patients with strong shadow intensity predominate: 68% compared to 32% with low intensity. The difference of 36% was statistically significant, p <0.001. Conversely, in conservative treatment, patients with low intensity (60%) were significantly more than those with high intensity (40%) of the shadow, p <0.001.

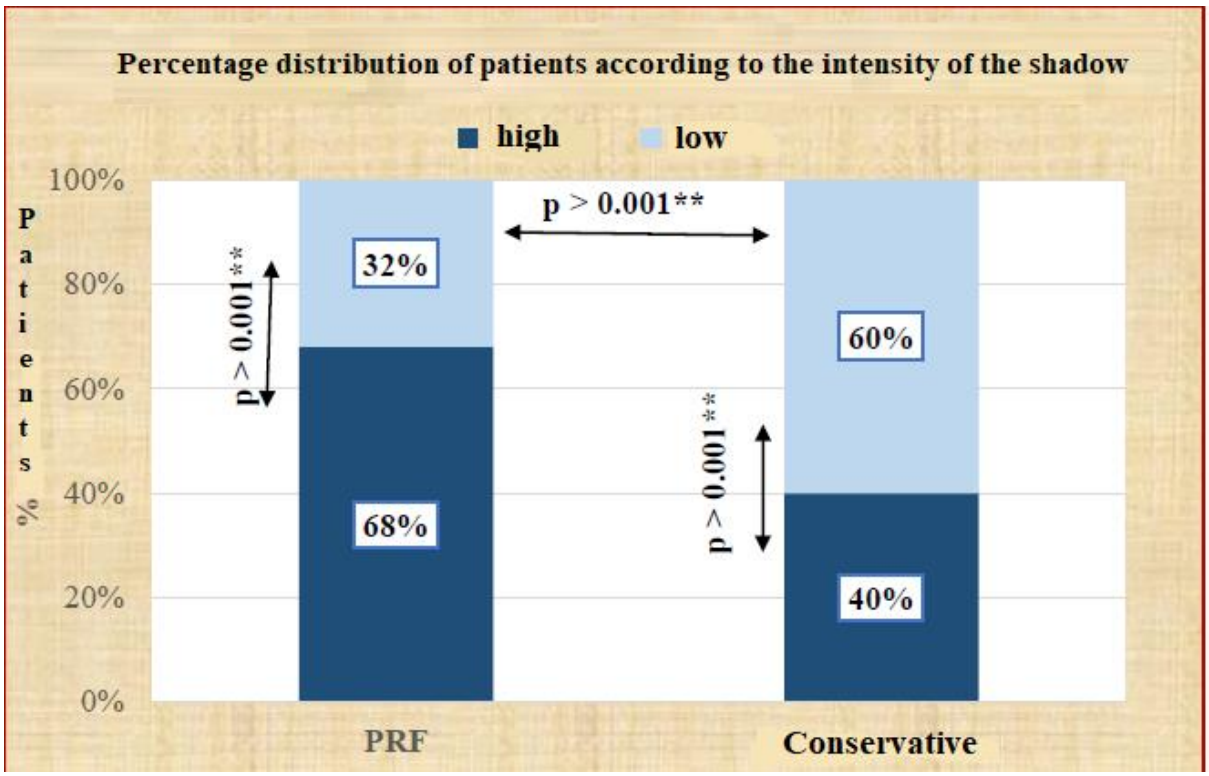


Fig.42. Percentage distribution of patients according to the intensity of the shadow

Separately for PRF treatment, the distribution according to the shadow intensity for the two jaws on the left and right is summarized in Table 9.

In the lower jaw, 70% of patients have a strong shadow intensity and 30% have a low shadow intensity. The difference is significant, p = 0.003. The distribution on the left and right side of the lower jaw is the same as the general distribution: 70% with strong intensity and 30% with low intensity.

In contrast to the lower jaw, there is a different distribution is observed in the left and right sides of the upper jaw.

Table 9: Distribution of patients according to the intensity of the shadow in the PRF group

PRF treatment	Intensity of the shadow		Fisher's test	
	strong	weak	difference	p
Lower jaw	**23**	**10**		

	(70%)	(30%)	40%	.003**
left	9	4		
	(70%)	(30%)	40%	.03*
right	14	6		
	(70%)	(30%)	40%	.02*
Upper jaw	**17**	**9**		
	(65%)	(35%)	30%	.03*
left	11	3		
	(78%)	(22%)	56%;.	.007**
right	6	6		
	(50%)	(50%)	0%	1.00

The distribution relative to the intensity of the shadow in the lower and upper jaw in patients undergoing PRF treatment is illustrated in Fig. 43.

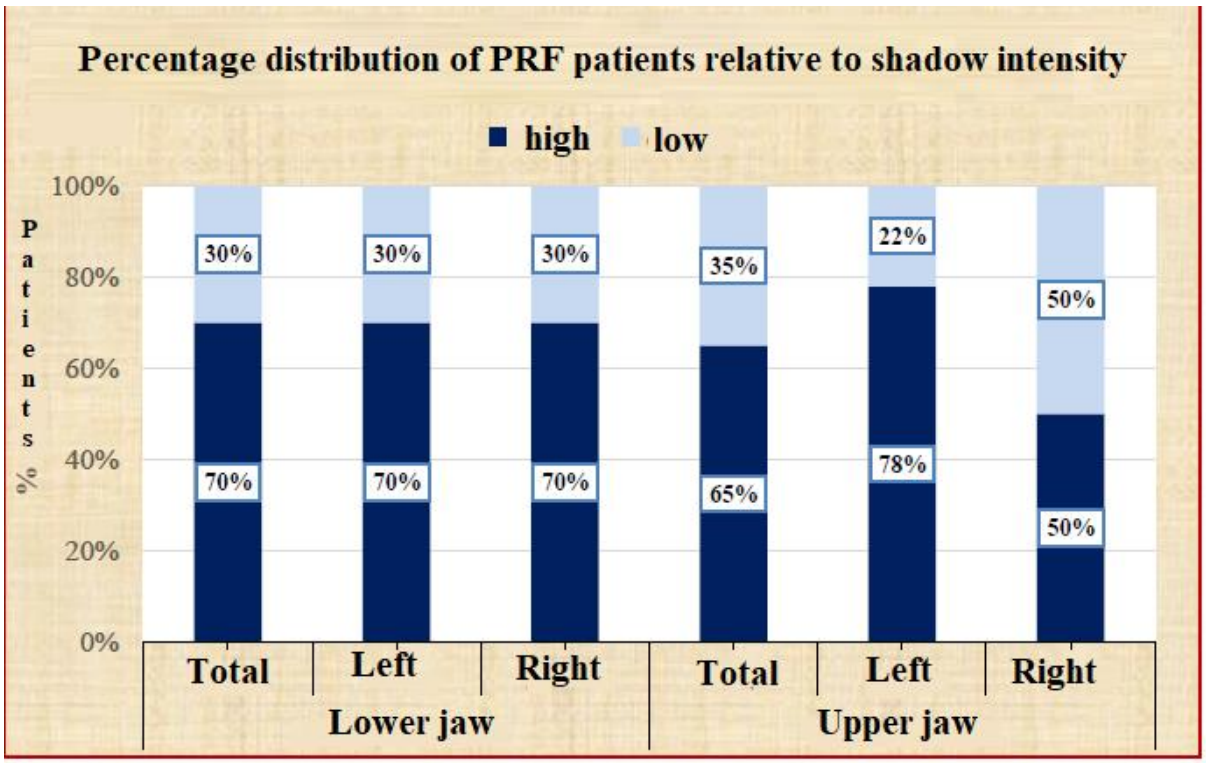


Fig. 43. Percentage distribution of PRF patients relative to shadow intensity

In conservative treatment, the distribution according to the intensity of the shadow for the upper and lower jaw on both sides of the jaws is summarized in Table 10. In the lower jaw, 39% of patients have a strong shadow intensity and 61% show a low intensity. The higher percentage of low intensity is statistically significant, p = 0.003. The distribution on both sides of the lower jaw is very similar. On the left side, 40% of patients have a high intensity and 60%

have a low intensity. On the right side, 38% are very intense, while 62% show low intensity. The results of patients with problems in the upper jaw indicate a predominant low intensity - 59% strong intensity - 41% of them. The difference of 24%, p = 0.040 is statistically significant. The distribution on the left and right sides of the jaw is similar. 40% of the patients with problems on the left have a strong intensity and 60% show a low intensity. The results of patients with problems on the right are similar - 42% have a strong intensity and 58% show a low intensity.

Table 10: Distribution of patients according to the intensity of the shadow in the group of conservative treatment

Conservative treatment	**Intensity of the shadow**		**Fisher's test**	
	strong	**weak**	**difference**	**p**
Lower jaw	**38**	**60**		
	(39%)	(61%)	(22%)	.003*+
left	18	27		
	(40%)	(60%)	(20%)	0.093
right	20	33		
	(38%)	(62%)	(24%	.019*
Upper jaw	**33**	**47**		
	(41%)	(59%)	18%)	.040*
left	15	22		
	(40%)	(60%)	(20%)	0.163
right	18	25		
	(42%)	(58%)	(16%)	0.195

Note: *The minus sign (-) in front of the value in the "difference" column indicates a higher percentage of patients with low shadow intensity.*

** Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

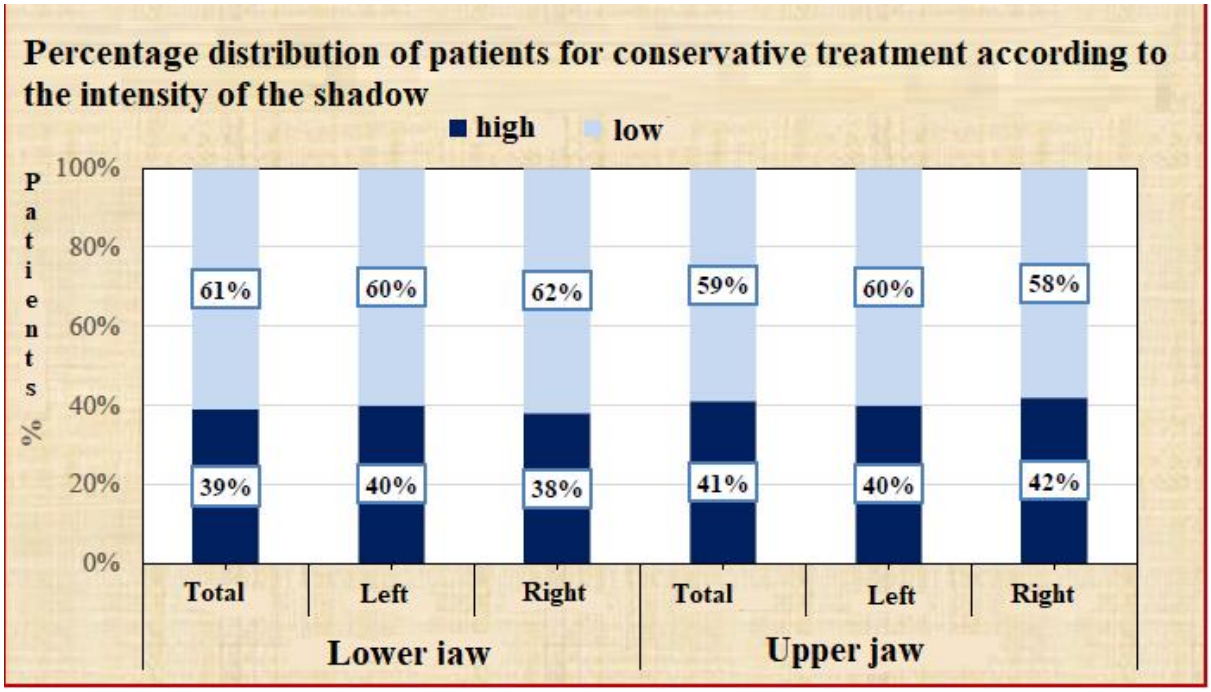


Fig. 44. Percentage distribution of patients for conservative treatment according to the intensity of the shadow

Distribution relative to homogeneity and presence of sequestration 6 months after treatment

Homogeneity was examined at 6 months after treatment. The percentage distribution of patients treated by both methods are presented in three categories: homogeneity, heterogeneity and presence of sequestration (Table 11). Homogeneity was found in 100% of patients on PRF treatment and in 69% of those on conservative treatment. The difference of 31% is statistically significant, p <0.001. Inhomogeneity was not observed in PRF patients, whereas in 31% of conservative patients. The difference is statistically significant, p <0.001. Presence of sequestration is shown by 100% of patients on PRF treatment and 22% of those on conservative treatment. The difference of 78% is statistically significant, p <0.001.

Table 11: Percentage distribution by homogeneity in both types of treatment

Homogeneity	Type of treatment		Fisher's test	
	PRF	Conservative	difference	p
homogeneity	59 (100%)	122 (69%)	31%	.000**
heterogeneity	0 0%	56 (31%)	-31%	.000**
presence of sequestration	59 (100%)	39 (22%)	78%	.000**

***Note**: The minus sign (-) before the value in the "difference" column indicates a higher percentage in conservative treatment. * Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

Figure 45 illustrates the homogeneity findings described above in both treatments.

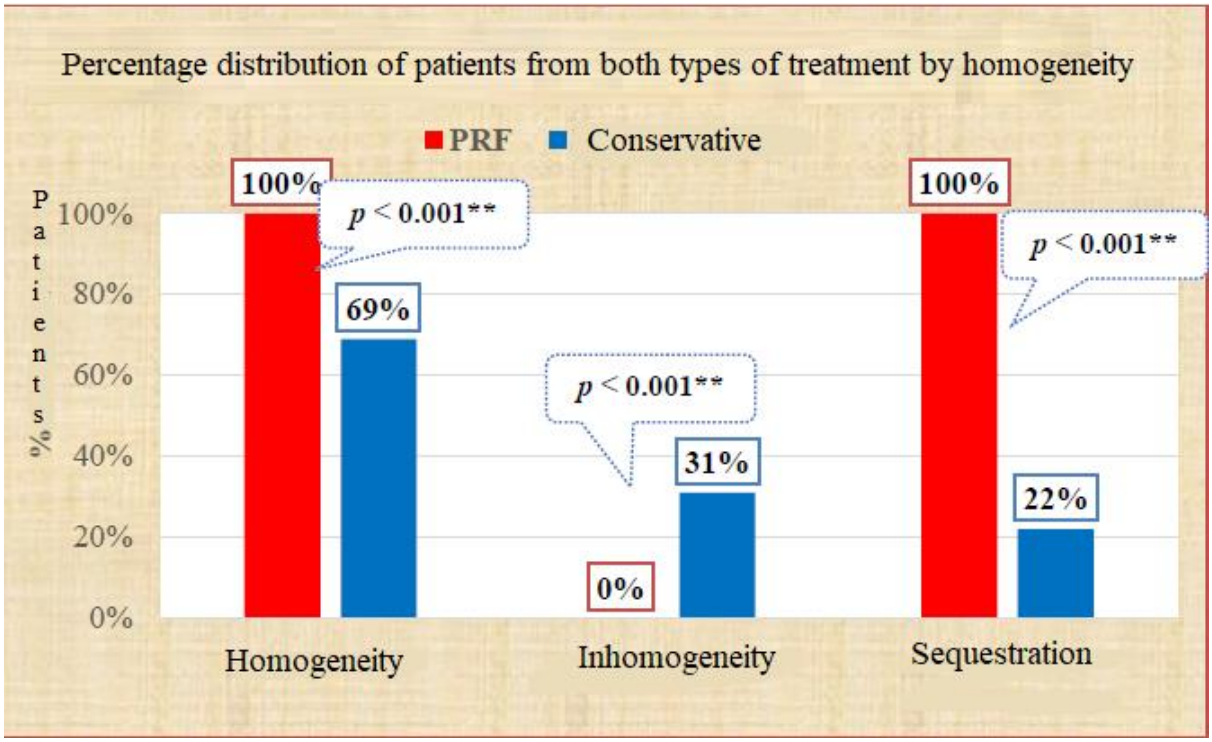


Fig. 45. Percentage distribution of patients from both types of treatment by homogeneity

The homogeneity distribution only for patients on PRF treatment is presented for the upper and lower jaws on both sides - left and right in Fig. 46. The equal values for homogeneity and sequestration in general, as well as for the left and right sides in both jaws are impressive. Values for inhomogeneity are completely absent. The percentage of homogeneity and sequestration is higher in the lower jaw (64%) compared to this percentage in the upper jaw (36%). In the lower jaw, the rate of homogeneity and sequestration on the left side (55%) is higher than on the right side (45%). In the upper jaw, the rate of homogeneity and sequestration was slightly lower on the left side (48%) than on the right side (52%).

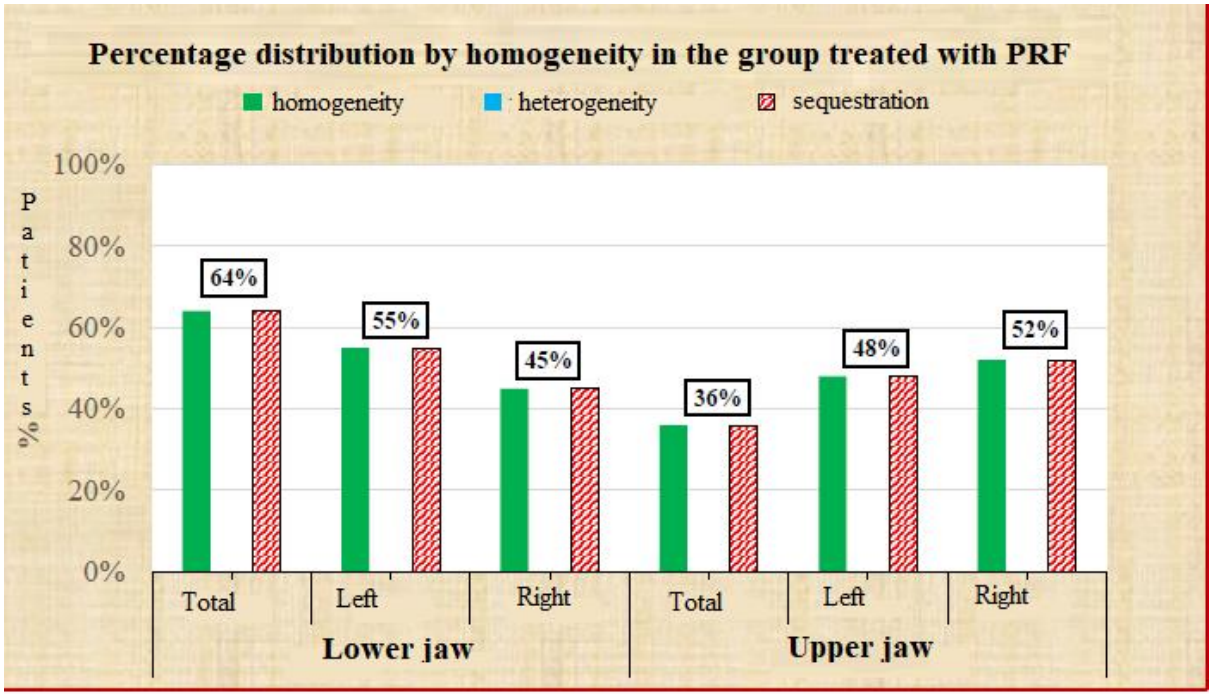


Fig. 46. Percentage distribution by homogeneity in the group treated with PRF

For patients with conservative treatment, the distribution by homogeneity is summarized in Fig. 47. Compared to the PRF-treated group, in conservative treatment the distribution varied between the three categories: homogeneity, heterogeneity, and sequestration.

The mandibular results 39% showed homogeneity, 22% heterogeneity and 16% sequestration. The results for the lower jaw show that the homogeneity on the left side (45%) is lower than that on the right side (55%). The distribution of inhomogeneity is reversed: 55% for the left and 45% for the right. Sequestration on the left is found in 43% of patients and on the right in 57% of them. The results of patients with upper jaw problems showed 30% homogeneity, 9% heterogeneity and 6% sequestration. Homogeneity on the left (53%) is higher than on the right (47%) and vice versa - heterogeneity is lower (38%) on the left and higher (62%) on the right. Sequestration is found in 45% of patients on the left and 55% of them on the right.

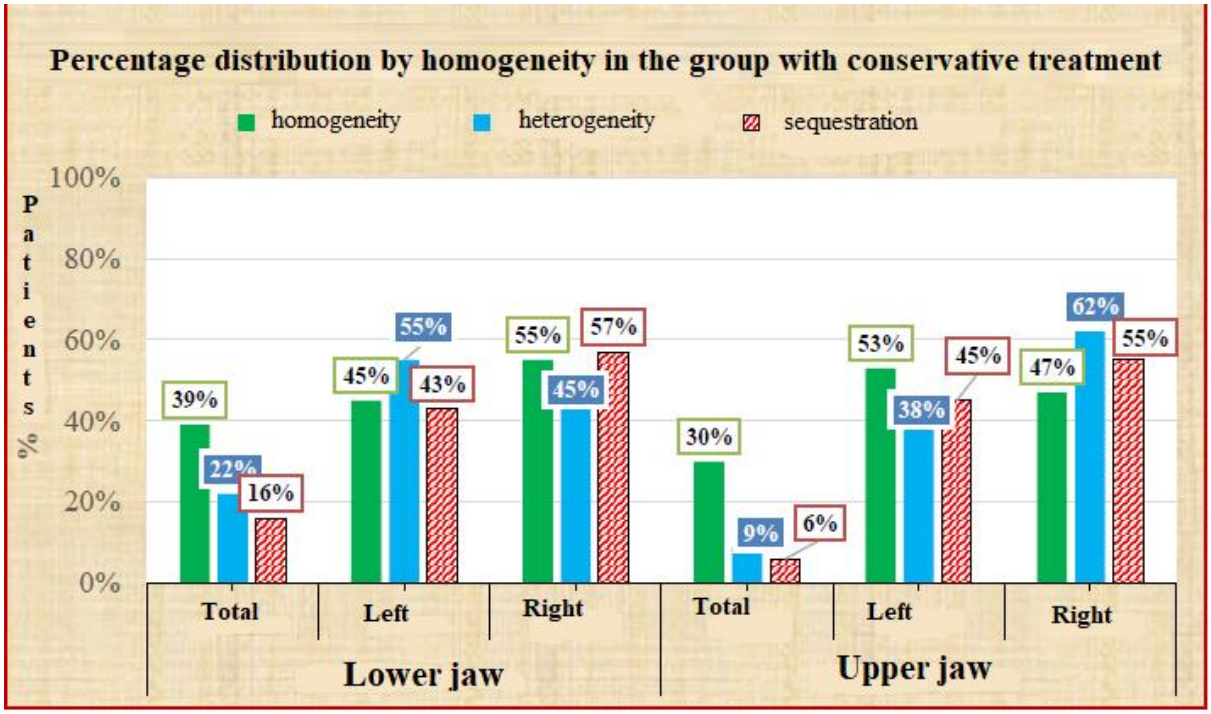


Fig. 47. Percentage distribution by homogeneity in the group with conservative treatment

Outlines and changes in the surrounding bone in both types of treatment

The distribution of patients from the two types of treatment according to the outlines is presented in four categories: abrupt, unsharp, intermittent and continuous (Table 12). Sharp outlines were found in 93% of PRF-treated patients and in 40% of conservatively treated patients. The difference of 53% is statistically significant, $p < 0.001$. Blurred outlines are present in 7% of patients with PRF treatment and in 60% of conservatively treated patients. The difference is statistically significant (53%), $p < 0.001$. Interrupted outlines were observed in 10% of patients treated with PRF and 66% of those treated conservatively, with a difference of 56%, $p < 0.001$.

Table 12: Outlines for both types of treatment

outlines	Type of treatment		Fisher's test	
	PRF	Conservative	difference	p
sharp outlines	55 (93%)	72 (40%)	53%	.000**
unsharp outlines	4 (7%)	106 (60%)	-53%	.000**
broken outlines	6 (10%)	117 (66%)	-56%	.000**
continuous outlines	53 (90%)	61 (34%)	66%	.000**

Note: *The minus sign (-) in front of the value in the "difference" column indicates a higher percentage in conservative treatment. * Statistical significance at $p < .05$; ** Statistical significance at $p \leq 0.01$*

Figure 48 shows the two trends: 1) In patients on PRF treatment, the outlines that predominate are sharp and continuous; 2) In patients on conservative treatment, blurred and interrupted outlines are more common.

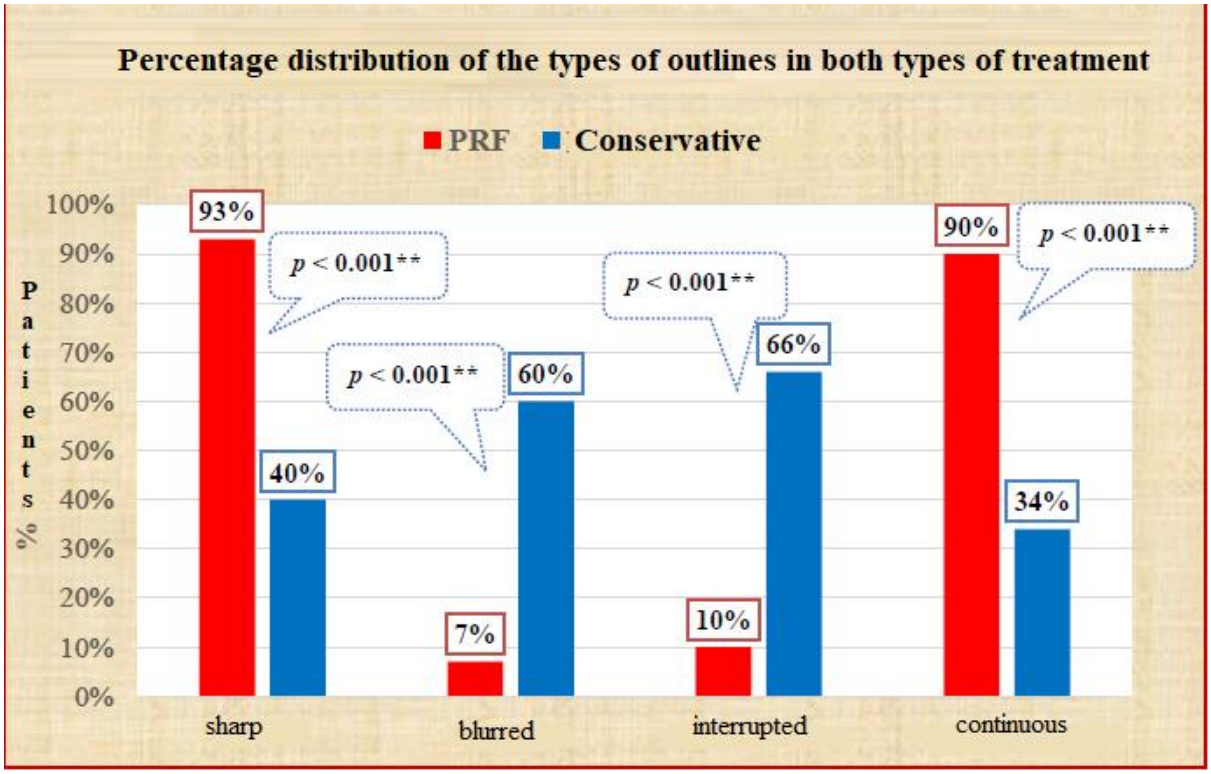


Fig. 48. Percentage distribution of the types of outlines in both types of treatment

The presence of changes in the surrounding bone was examined at 6 months after treatment. This was found in 18% of patients on conservative treatment and was not observed in patients on PRF treatment (Figure 49). The difference between the two treatments is statistically significant, p <0.001.

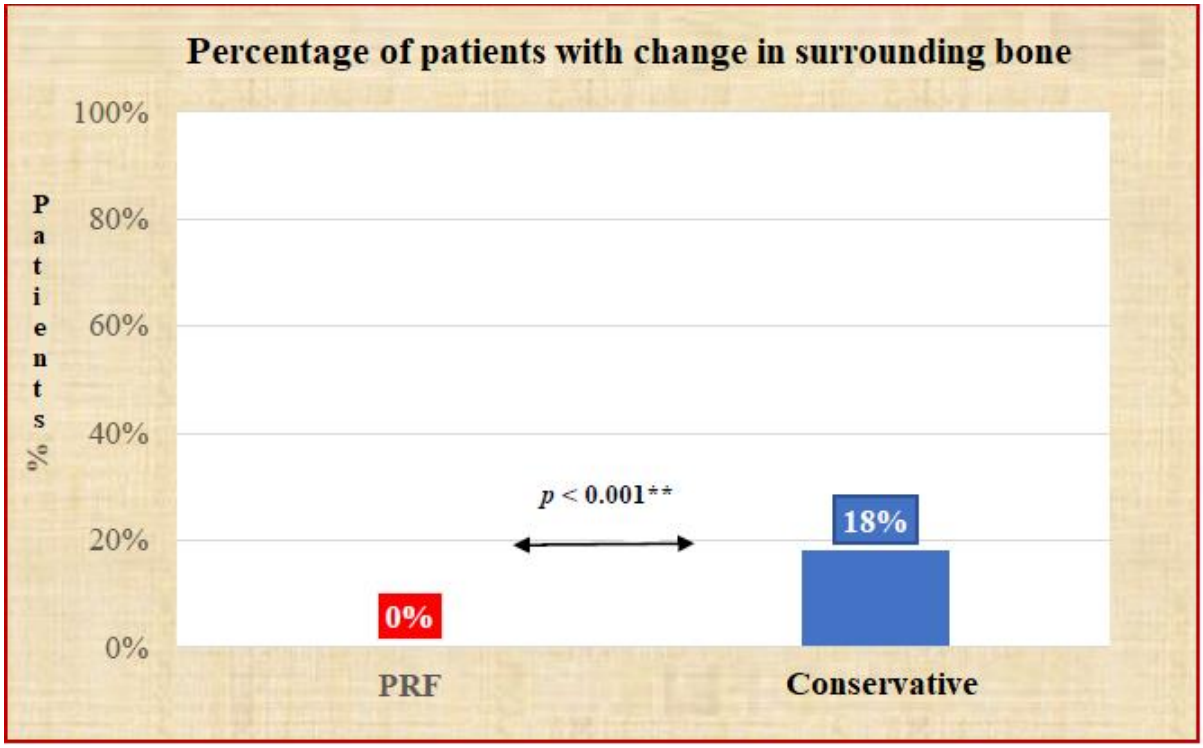


Fig. 49. Percentage of patients with change in surrounding bone

Summary of the results to the second task

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.

3. Results on the third task

The X-ray evaluation includes the following parameters: osteolysis and bone loss, bone density, buccal width and lingual width.

Bone density and osteolysis were monitored at four time points: before treatment, on the 14th, 30th and 90th day. Buccal width and lingual width were measured on the 45th and 90th day after treatment.

Results are presented as mean and standard deviation. The statistical comparison of the two groups of patients at different time points was made by t-test for independent samples. Intragroup development in the mean values of the parameters was monitored over time by t-test for dependent samples

X-ray evaluation of osteolysis and bone loss

The change in mean osteolysis in both treatments can be seen in Table 13. It can be seen that prior to treatment, the PRF-treated group had a slightly higher mean than the conservative treatment group, but the difference (0.07) was minimal and not statistically significant, p = 0.89. On the 14th day, the conservative treatment group showed a higher value, but again with a minimal difference (0.08) without statistical significance, p = 0.77. On the 30th day, the values were very similar without significant difference, p = 0.86. Only on the 90th day there was a significant difference between the two types of treatment, p = 0.049. A higher mean (= 8.97) was observed in PRF treatment compared to that (9.98) in conservative treatment.

Table 13: Comparison of patients on PRF treatment and conservative treatment on osteolysis and bone loss

Osteolysis and bone loss	Type of treatment		T test		
	PRF	Conservative	difference	t	P
Before treatment	10.05 80	9.98 ± 2.24	0.07	24	0.89
14th day	9.25* 1.91	9.33 ±1.76	-0.08	-0.28	0.77
30th day	7.77*1.78	7:72±2.10	0.05	0.18	0.86
90th day	8.97 Ц 1.82	8.39 ±2.26	0.58	1.99	.049*

Note: *The minus sign (-) in front of the value in the "difference" column indicates a higher mean value in conservative treatment. * Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

The intragroup and intergroup dynamics in the values of osteolysis before treatment, on the 14th, 30th and 90th day after treatment is illustrated in Fig. 50. It outlines a similarity between the two groups of patients. In the first three time points, the values are very similar and the graphs overlap. Only on the 90th day, a slight difference was seen, with a higher value in PRF treatment, as already described in the previous paragraph. There is also a tendency to decrease the values of osteolysis in both groups.

The intragroup values of the group treated with PRF decreased from 10.05 before treatment to 9.25 on the 14th day. The difference (= 0.80) is statistically significant, p = 0.002. On the 30th day, the value decreased to 7.77, with a significant difference of 1.48, p <0.001. On the 90th day, the average value increased to 8.97. The difference of 1.20 is also statistically significant, p <0.001.

A similar downward trend in the mean value of osteolysis was observed in the conservative treatment group at the first three time points. On day 14, a mean value of 9.33 was reported, which was 0.65 lower than before surgery. The difference is significant, p <0.001. On the 30th day, a mean value of 7.72 was found, with a significant decrease of 1.61, p <0.001. On the 90th day, similar to the PRF-treated group, there was a significant increase of 0.67 units and the mean value reached 8.39, p <0.001.

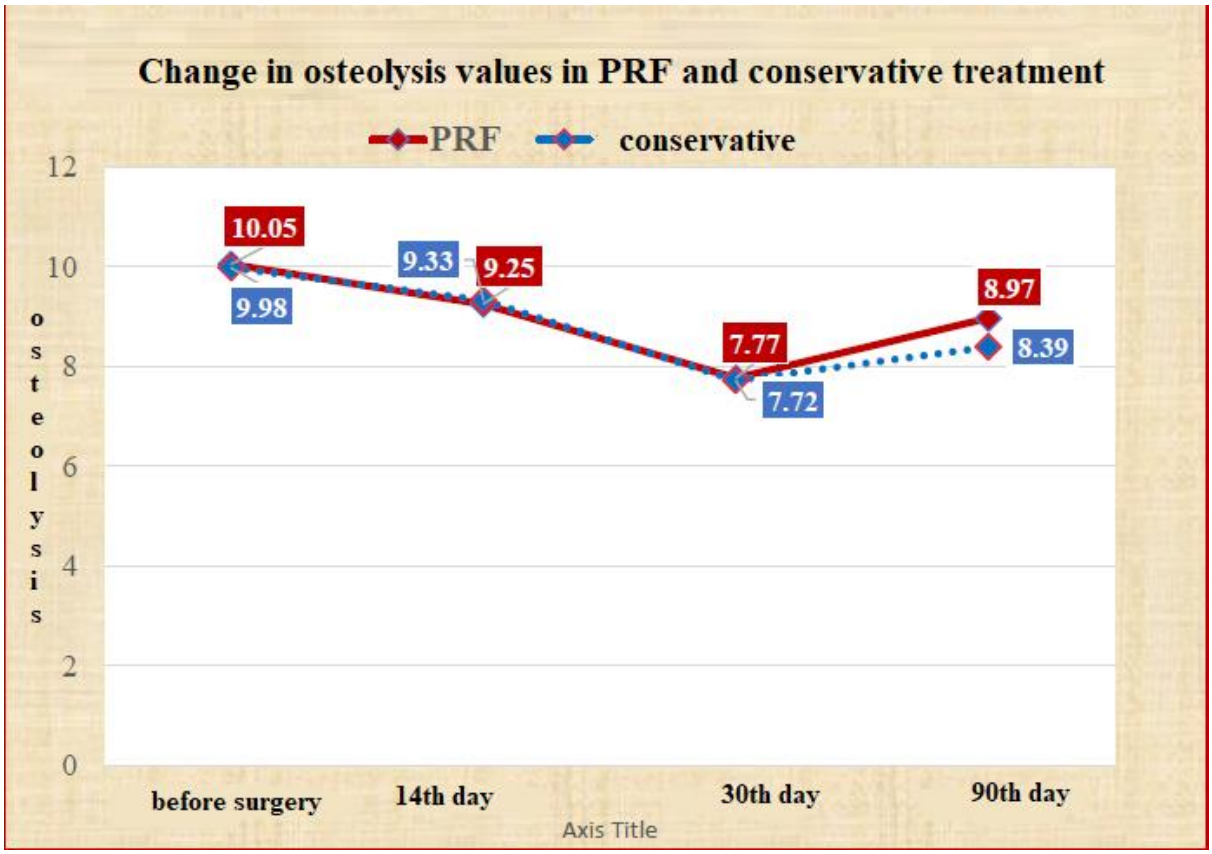


Fig. 50. Change in osteolysis values in PRF and conservative treatment

X-ray evaluation of bone density

A comparison of the two groups of patients in terms of bone density showed no significant difference before treatment, with mean values of 101.91 (PRF treatment) and 104.52 (conservative treatment), p = 0.65 (Table 14). On the 14th day, change occurred and bone density in patients with PRF treatment was significantly higher by 26.10, p <0.001. On the 30th

day, a higher value was again reported in the PRF group, with a significant difference of 36.24 units, p <0.001. On the 90th day, the difference between the two groups widened. The value of bone density in the PRF group reached 159.17 and was 67.85 higher than that of the group with conservative treatment (91.32), p <0.001.

Table 14: Comparison of PRF patients and conservative treatment regarding bone density

Bone density	Type of treatment		T test		
	PRF	Conservative	difference	t	P
Before treatment	101.91 ±40.28	104.52 ± 43.54	-2.61	0.44	0.65
14th day	128.76 ±37.45	102.66±36.68	26.1	4.66	.000**
30th day	135.66± 39.13	99.42 ±47.64	36.24	5.83	.000**
90th day	159.17 ± 31.04	91.32 ±36.35	67.85	13.92	.000**

Note: *The minus sign (-) in front of the value in the "difference" column indicates a higher mean value in conservative treatment. * Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

While the development of osteolysis in the two groups showed a similar trend, two different trends in bone density emerged. Intra-group and intergroup development of bone density before treatment, on days 14, 30, and 90 after treatment, is illustrated in Fig. 51. While PRF treatment showed an increase in mean bone density, conservative treatment occurred decrease.

The intragroup distribution in the PRF-treated group, on the 14th day, increased from 104.52 to 128.76. The increase of 26.85 was statistically significant, p <0.001. On the 30th day, a new increase of 6.9 occurred, but the value of the increase was not significant, p = 0.178. On the 90th day, an increase of 23.51 is reported again. This increase was statistically significant, p <0.001.

In the conservative treatment group, on the 14th day, there was a decrease in mean bone density from 104.52 to 102.66. The decrease of 1.86 units is not statistically significant, p = 0.55. The value continued to decrease to 99.42 on the 30th day, but the decrease of 3.24 units was not significant, p = 0.29. On the 90th day, bone density had the lowest value (91.32), with a significant difference value of 8.1, p = 0.004.

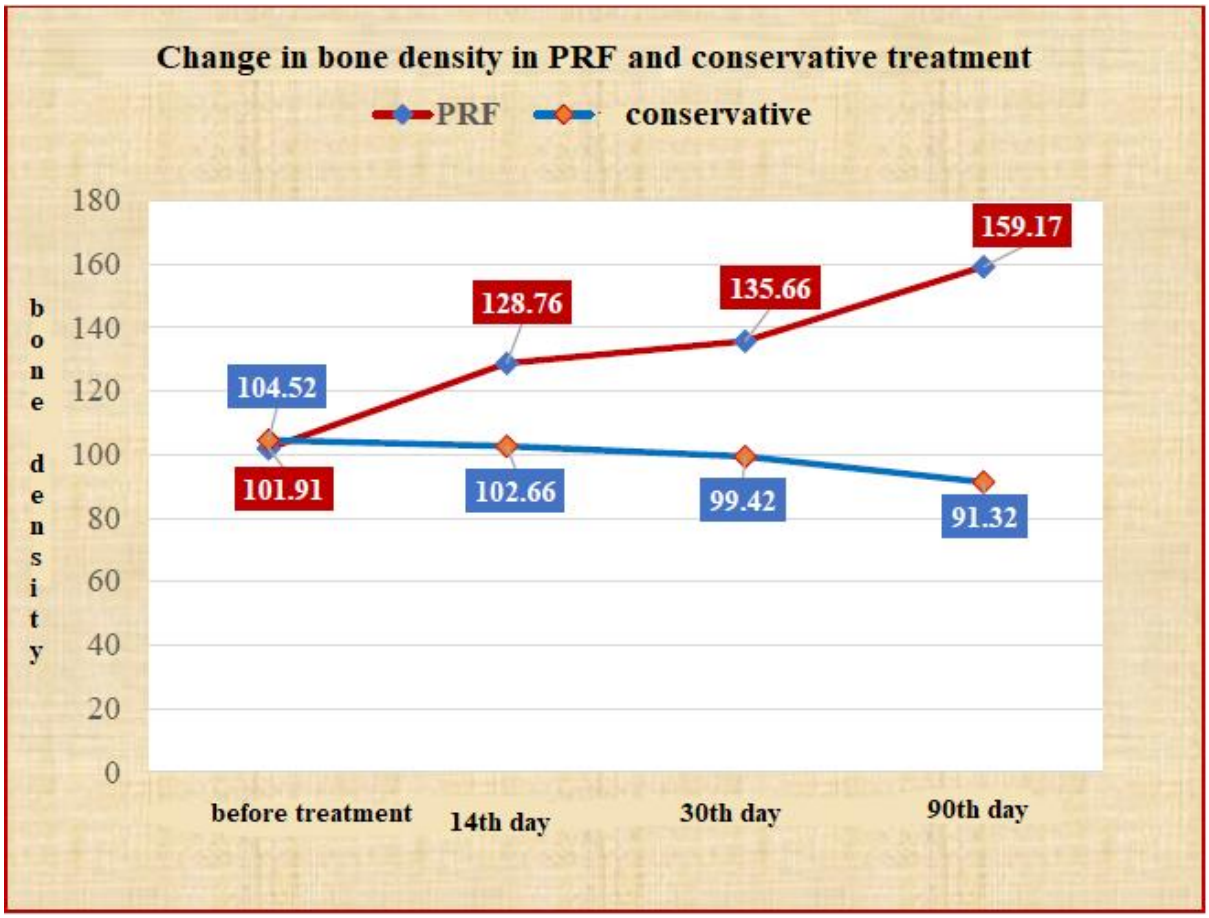


Fig. 51. Change in bone density in PRF and conservative treatment

X-ray evaluation of buccal and lingual width

Buccal width was measured at two time points - on the 45th and 90th day after treatment. The results are summarized in Table 15. On 45th day, the PRF group had a mean buccal width of 1.50 mm, while the conservative treatment group showed a value of 0.62 mm. The difference of 0.88 mm is statistically significant, p <0.001. On the 90th day, the opposite trend was observed - the average value in the conservative treatment (1.34 mm) was higher by 0.12 mm than that of the PRF group, with a significant difference, p = 0.016.

Table 15: Comparison of patients with PRF and conservative treatment regarding buccal width

Buccal Width (mm)	Type of treatment		T test		
	PRF	Conservative	difference	t	P
45th day	1.50 ±0.48	0.62 ±0.13	0.88	13.91	.000**
90th day	1.22 ±0.26	1.34 ±0.48	-0.12	2.43	.016*

***Note**: The minus sign (-) in front of the difference value indicates a higher mean value in conservative treatment. * Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

The intergroup and intragroup dynamics in buccal width values are illustrated in Fig. 52. The difference between the two groups of patients is clear. While in PRF treatment, the

value decreased significantly from 1.5 mm on the 45th day to 1.22 mm on the 90th day (p <0.001), in the conservative treatment group, the value increased significantly from 0.62 mm on day 45 to 1.22 mm on day 90, p <0.001.

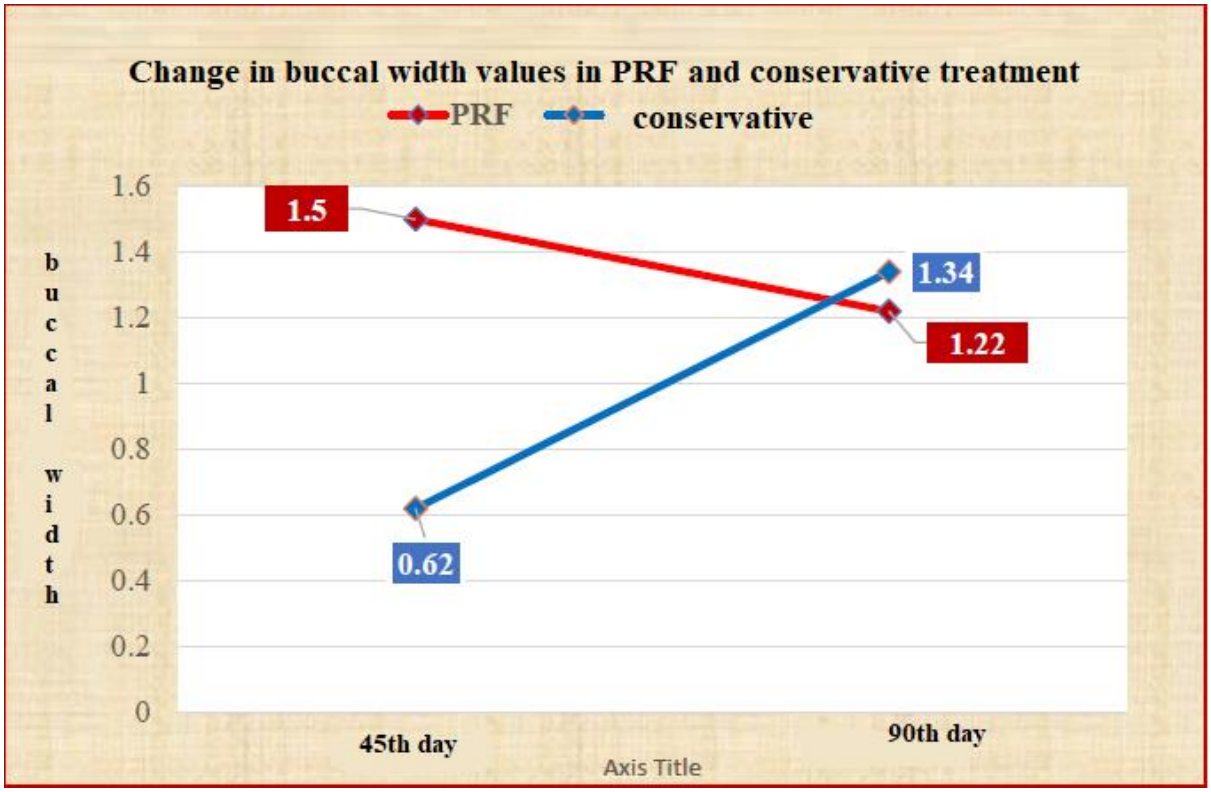


Fig. 52. Change in buccal width values in PRF and conservative treatment

Lingual width was also measured at two time points, on the 45th and 90th day. Both dimensions show a significantly higher value in PRF treatment. On the 45th day, the mean value of the PRF group was 2.44 mm, while that of conservative treatment was 1.40 mm. The difference of 1.04 mm is statistically significant, p <0.001. At day 90, PRF patients showed a mean linear width of 2.13 mm, and those with conservative treatment had a value of 1.48 mm, with a significant difference of 0.65 mm (p <0.001).

Table 16: Comparison of patients with PRF and conservative treatment regarding lingual width

Linval width (mm)	Type of treatment		T test		
	PRF	Conservative	difference	t	P
45th day	2.44 ±0.98	1.40 ±0.43	1.04	7.9	.000*+
90th day	2.13 ± 0.48	1.48 ±0.41	0.65	9.33	.000*

** Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

The change in lingual width values at both time points in the two treatments can be seen in Fig. 53. A different trend is emerging from treatment type. In the PRF group there was a significant decrease from 2.44 mm to 2.13 mm (p = 0.004), while in conservative treatment the value decreased from 1.40 mm on the 45th day to 1.48 mm on the 90th day, with a significant difference of 0.08, p = 0.012 .

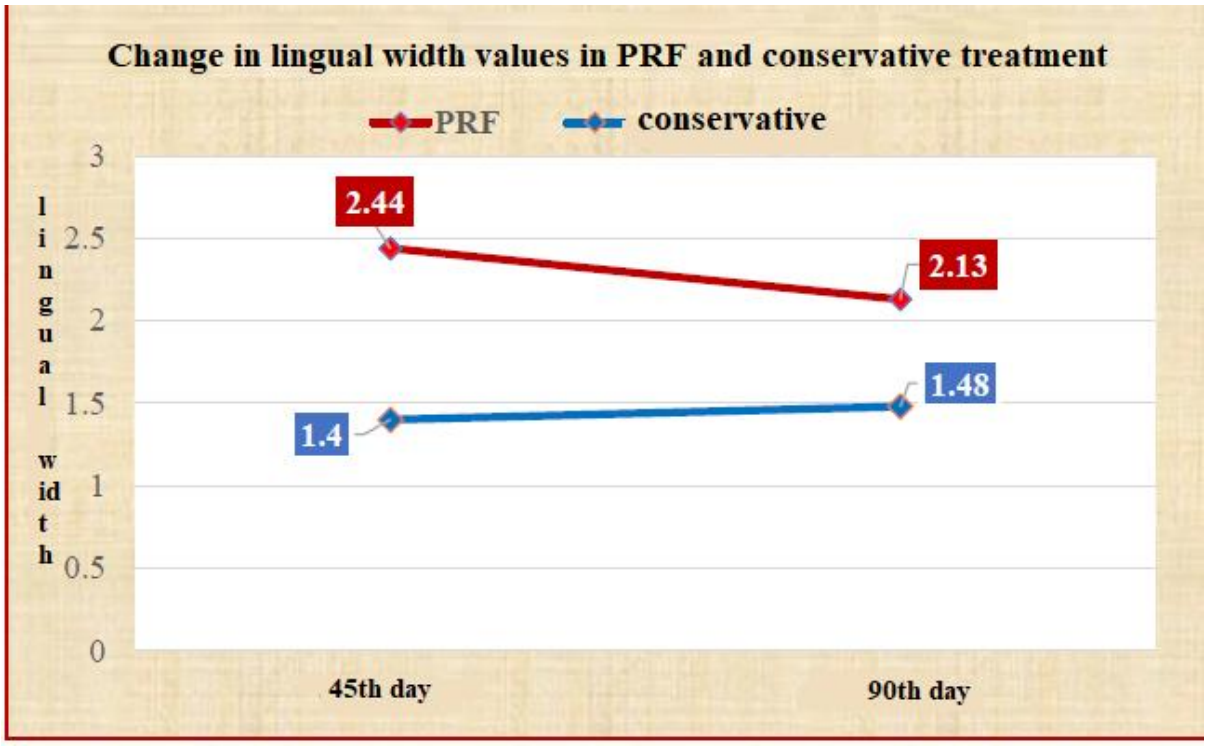


Fig. 53. Change in lingual width values in PRF and conservative treatment

Summary of the results to the third task

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.

4. Results on the fourth task

In the fourth task, clinical indicators were monitored in both groups of patients, those treated surgically with PRF and those treated conservatively, at five points in time: immediately after the intervention; on the 7th, 14th, 30th and 90th day after the intervention. Clinical indications include redness, swelling, healthy granulation tissue and signs of epithelialization.

Presence of redness

The results of the comparison of the two groups of patients regarding the presence of redness are summarized in Table 17. Immediately after the intervention, redness was observed in 100% of patients, regardless of the method of treatment. On the 7th day after the intervention, 86% of patients with PRF had redness and 89% of those with conservative treatment. The difference of 3% is not statistically significant, p = 0.636.

On the 14th day, patients with flushing in the PRF group accounted for 22% and those in the conservative treatment group for 63%. The difference of 41% was statistically significant, p <0.001. On the 30th day, the percentage of patients with flushing in the PRF group decreased to 3% and that in the conservative treatment group to 26%, with a significant difference of 23%, p <0.001. On the 90th day, no redness was observed in the PRF group (0%), and in the conservative group it was reported in 12% of patients, with a significant difference, p = 0.003.

Table 17: Comparison of PRF patients and conservative treatment for the presence of redness

Tracking redness	Type of treatment		Fisher's test	
	PRF	Conservative	difference	p
After treatment	59	178		
	(100%)	(100%)	0%	
7th day	51	159		
	(86%)	(89%)	*-3%*	0.636
14th day	13	113		
	(22%)	(63%)	-41%	.000**
30th day	*2*	46		

	(3%)	(26%)	-23%	.000**
90th day	0	21		
	0%	(12%)	-12%	.003**

*Note: The minus sign (-) in front of the value in the "difference" column indicates a higher percentage in conservative treatment. * Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

The change in the percentage of patients with redness in the PRF group at the five time points can be observed in Fig. 54. Immediately after the intervention, redness was observed in 100% of the patients. On the 7th day, a decrease of 86% was reported and the difference of 14% with the starting point was statistically significant, p = 0.006. On the 14th day, redness was observed in 22% of patients. There was a 62% reduction on the 7th day, which was statistically significant, p <0.001. On the 30th day, only 3% of patients had flushing, with a 19% significant reduction on day 14, p = 0.004. Between the 30th and 90th day, the redness decreased to 0%, but the difference of 3% was not significant, p = 0.496.

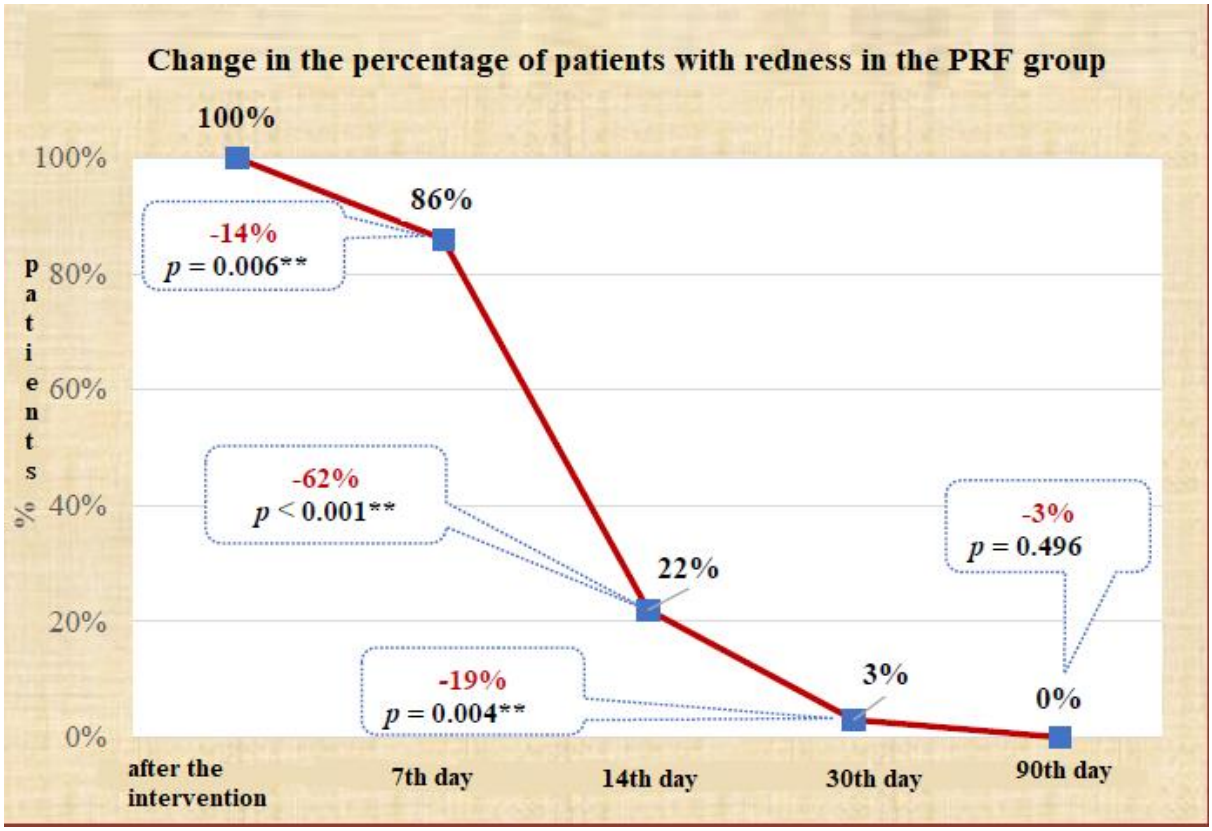


Fig. 54. Change in the percentage of patients with redness in the PRF group

In the conservative treatment group, there was also a significant reduction in the percentage of patients with redness from baseline to the 90th day (Fig. 55). Similar to the PRF group, immediately after the intervention, redness was observed in 100% of patients. On the 7th day, there was a decrease of 89%, with a significant difference of 11%, p <0.001. On the

14th day, redness was observed in 63% of patients, with a decrease of 26% on the 7th day, which was statistically significant, p <0.001. On the 30th day, 26% of patients had flushing, with a 37% significant reduction on day 14, p <0.001. Between the 30th and 90th day, the redness decreased to 12% with a significant difference of 14% is significant, p = 0.001.

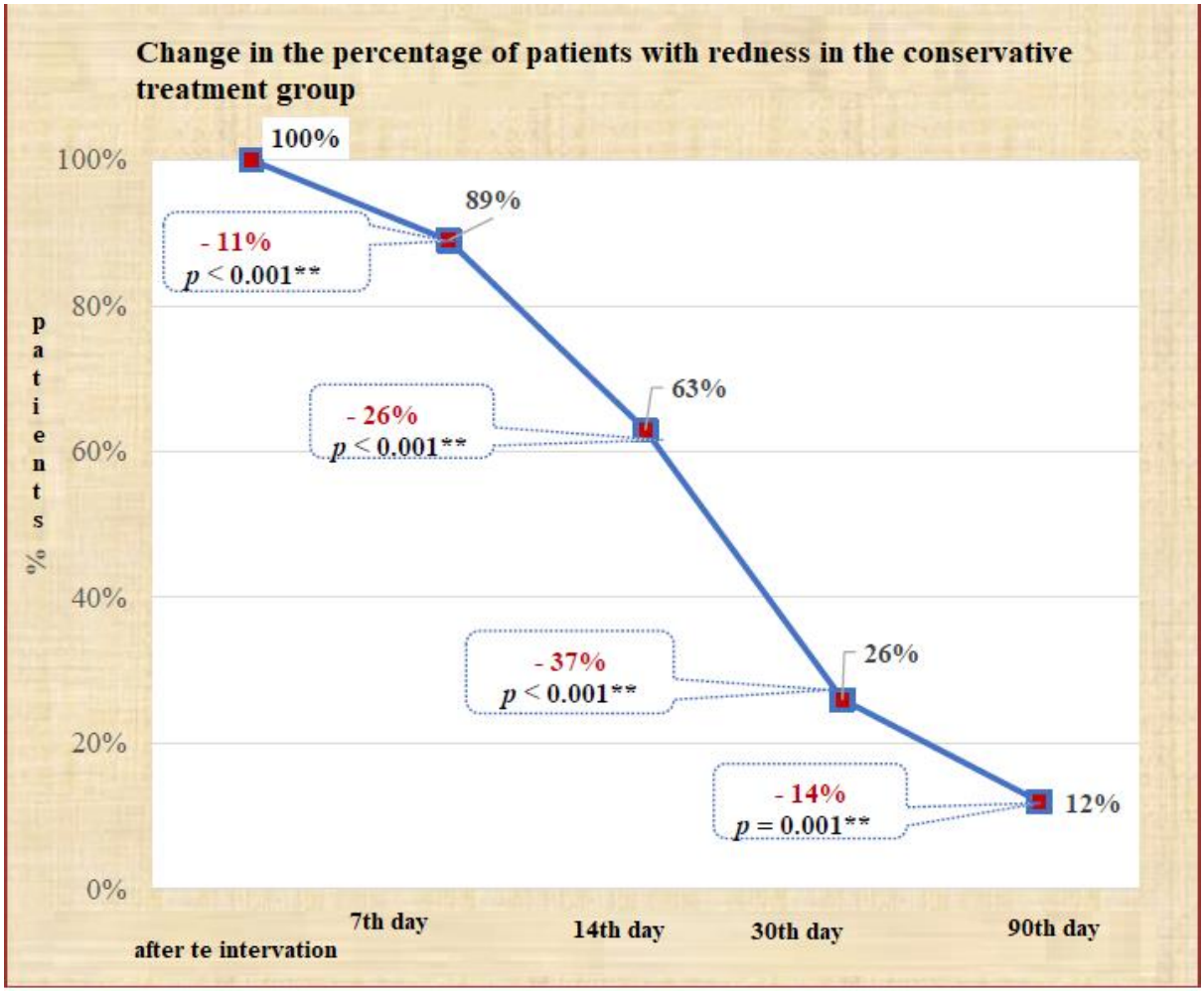


Fig. 55 Change in the percentage of patients with redness in the conservative treatment group

The presence of edema

Follow-up of edema was performed at the same five starting points: after the intervention, on the 7th, 14th, 30th and 90th day after the intervention. The results are summarized in Table 18. Immediately after the intervention, edema was observed in both groups in 100% of patients. On the 7th day, the percentage decreased to 69% in the PRF group and 58% in patients undergoing conservative treatment. The percentage of edema in the conservative group was 11% lower, but the difference was not statistically significant, p = 0.126.

On the 14th day, edema was observed in 3% of PRF patients and in 19% of those treated conservatively. The difference of 16% is statistically significant, p = 0.003. On the 30th day, only 3% of patients had edema, with a 19% significant reduction relative to the 14th day, p =

0.004. Between the 30th and 90th day, the swelling decreased to 0%, but the difference of 3% was not significant, p = 0.496. On the 30th day, none of the patients with PRF treatment had edema (0%), and in the group with conservative treatment, edema was observed in only 2%. The difference is minimal and not statistically significant, p = 0.576. On the 90th day, there were no edema patients in either group.

Table 18: Comparison of PRF patients and conservative treatment for the presence of edema

Tracking edema	Type of treatment		Fisher's test	
	PRF	Conservative	difference	p
After treatment	59	178		
	-100%	-100%	0%	-
7th day	41	103		
	-69%	-58%	11%	0.126
14th day	2	34		
	-3%	-19%	-16%	*.003***
30th day	0	3		
	0%	-2%	-2%	*0.576*
90th day	0	O		
	(0%	0%	0%	-

Note: *The minus sign (-) in front of the value in the "difference" column indicates a higher percentage in conservative treatment. * Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

The intragroup dynamics in the presence of edema is presented in Figures 56 and 57. Figure 56 shows the development in the PRF-treated group. Between the starting point and the 7th day, there is a reduction in swelling from 100% to 69%. The decrease of 31% is statistically significant, p <0.001. Between the 7th and 14th day, a new significant reduction from 66% to 3% was observed, p <0.001. On the 30th day, the swelling disappears completely and this condition persists until the 90th day.

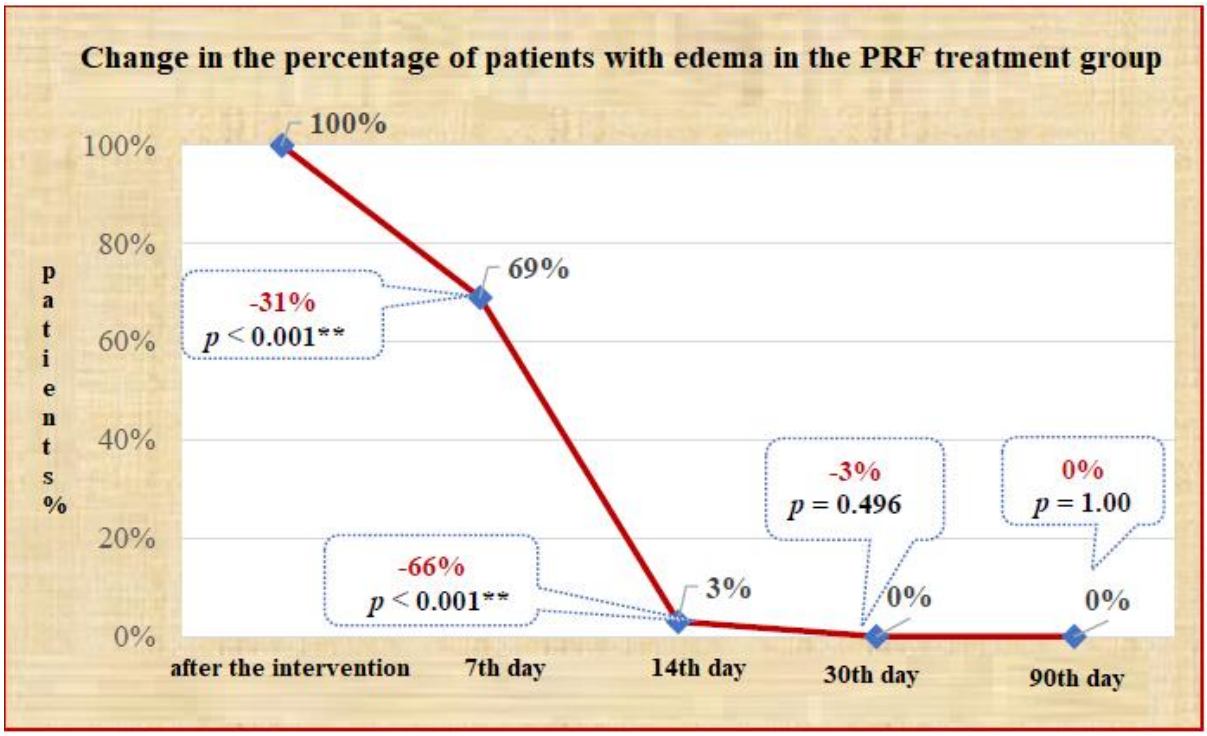


Fig. 56. Change in the percentage of patients with edema in the PRF treatment group

The intragroup dynamics in conservative treatment patients is illustrated in Fig. 57. Immediately after the intervention, edema was observed in 100% of the patients in this group. On the 7th day, it decreased to 58%, with a significant difference of 42%, p <0.001. At the 14th day, patients with edema accounted for only 19%. Compared with the 7th day, there is a significant decrease of 39%, p <0.001. On the 30th day, only 2% of patients had edema with a 17% significant difference from the 14th day, p <0.001. On the 90th day, the swelling disappeared in all patients undergoing conservative treatment.

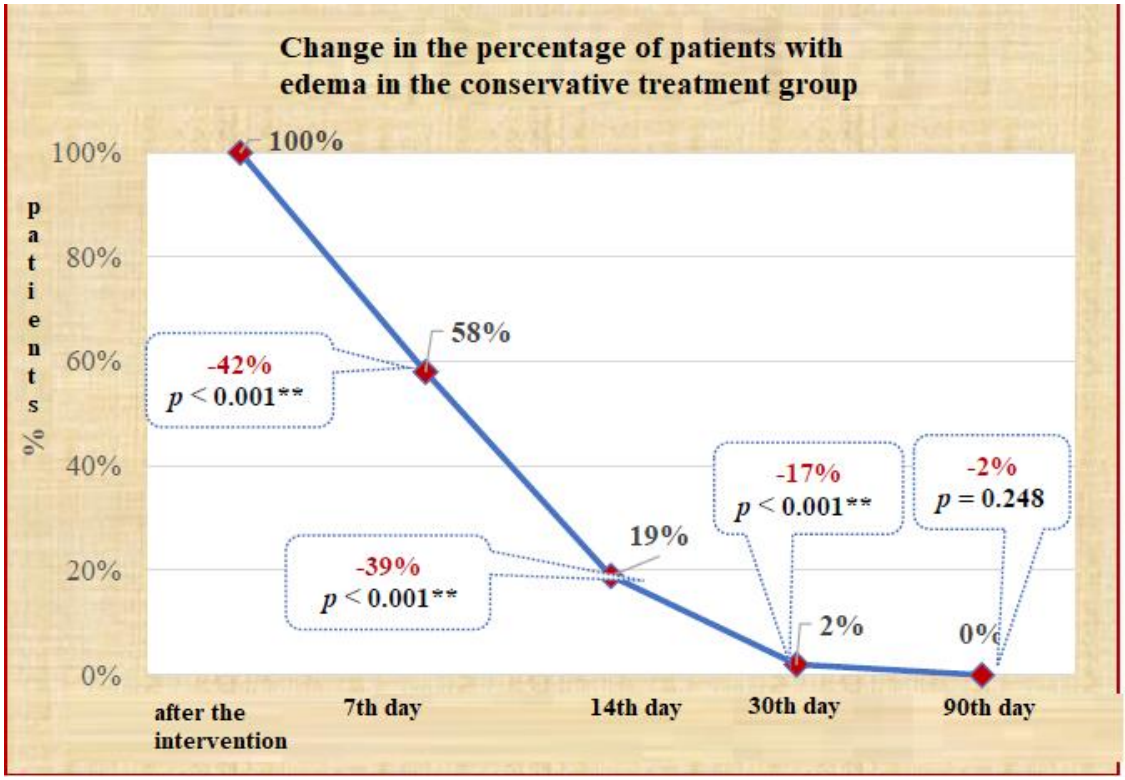


Fig. 57. Change in the percentage of patients with edema in the conservative treatment group

Presence of healthy granulation tissue

The presence of healthy granulation tissue in both groups of patients was monitored at five time points. The results are summarized in Table 19. Immediately after the intervention, healthy granulation tissue was not found in any of the patients, regardless of the type of treatment. On the 7th day, it was observed in 86% of the PRF group and in 83% of the group with conservative treatment, without significant difference, p = 0.683. On the 14th day, healthy granulation tissue was observed in 100% of the PRF group and 94% of that with conservative treatment. The difference of 6% is not significant, p = 0.07. On the 30th and 90th day, healthy granulation tissue was found in all patients, regardless of the type of treatment.

Table 19. Comparison of patients with PRF and conservative treatment regarding the presence of healthy granulation tissue

Monitoring of healthy granulation tissue	Type of treatment		Fisher's test	
	PRF	Conservative	difference	p
After treatment	0	0		
	0%	0%	0%	-
7th day	51	148		
	(86%)	(83%)	3%	0.683
14th day	59	167		
	(100%)	(94%)	6%	0.07
30th day	59	178		

	(100%)	(100%)	0%	-
90th day	59	178		
	(100%)	(100%)	0%	-

The change in the presence of healthy granulation tissue for the PRF treatment group can be traced in Fig. 58. Immediately after the intervention, healthy tissue was not found in any of the patients in this group. On the 7th day, a significant change occurred, with healthy granulation tissue observed in 86% of the group, p <0.001. On the 14th day, healthy granulation tissue was found in all (100%) patients. The increase of 14% is statistically significant, p = 0.006. On the 30th and 90th day there is no change, in all patients there is a healthy granulation tissue.

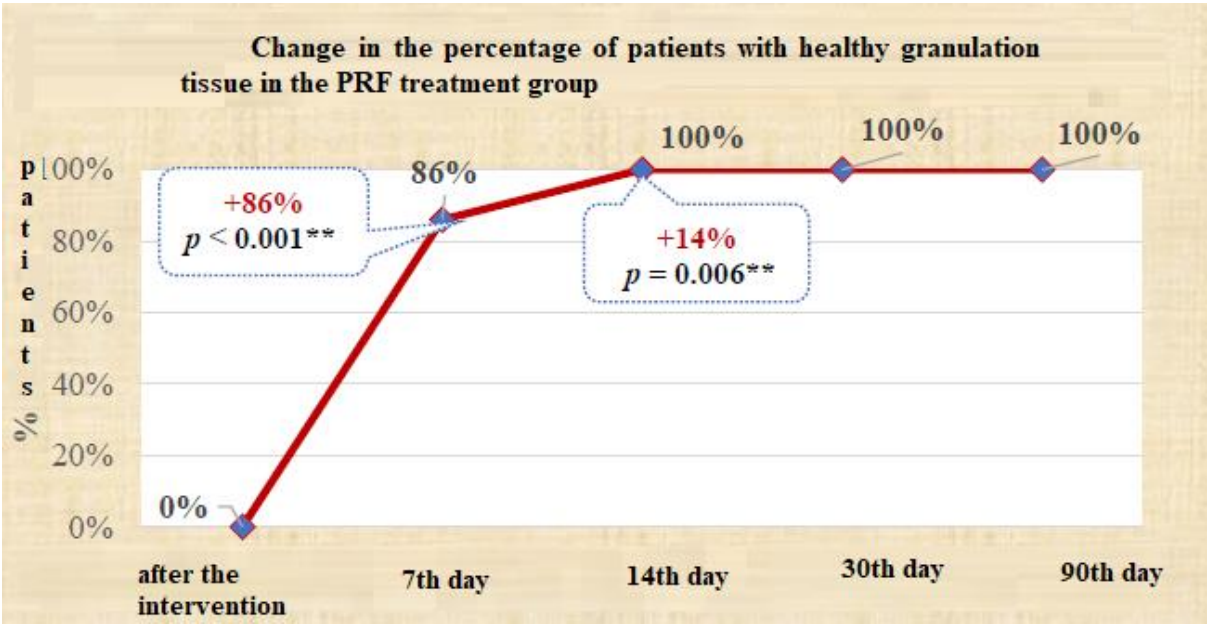


Fig. 58. Change in the percentage of patients with healthy granulation tissue in the PRF treatment group

In the conservative treatment group (Fig. 59), no healthy tissue was found in any of the patients immediately after the intervention. On the 7th day, it was present in 83% of patients, with a significant percentage increase, p <0.001. On the 14th day, 94% of the examined patients showed healthy granulation tissue. The increase of 11% was statistically significant, p = 0.002. On the 30th day, healthy granulation tissue was present in all patients, with a significant increase of 6% compared to the 14th day, p = 0.01. On the 90th day, no change is observed, 100% presence of healthy tissue is preserved.

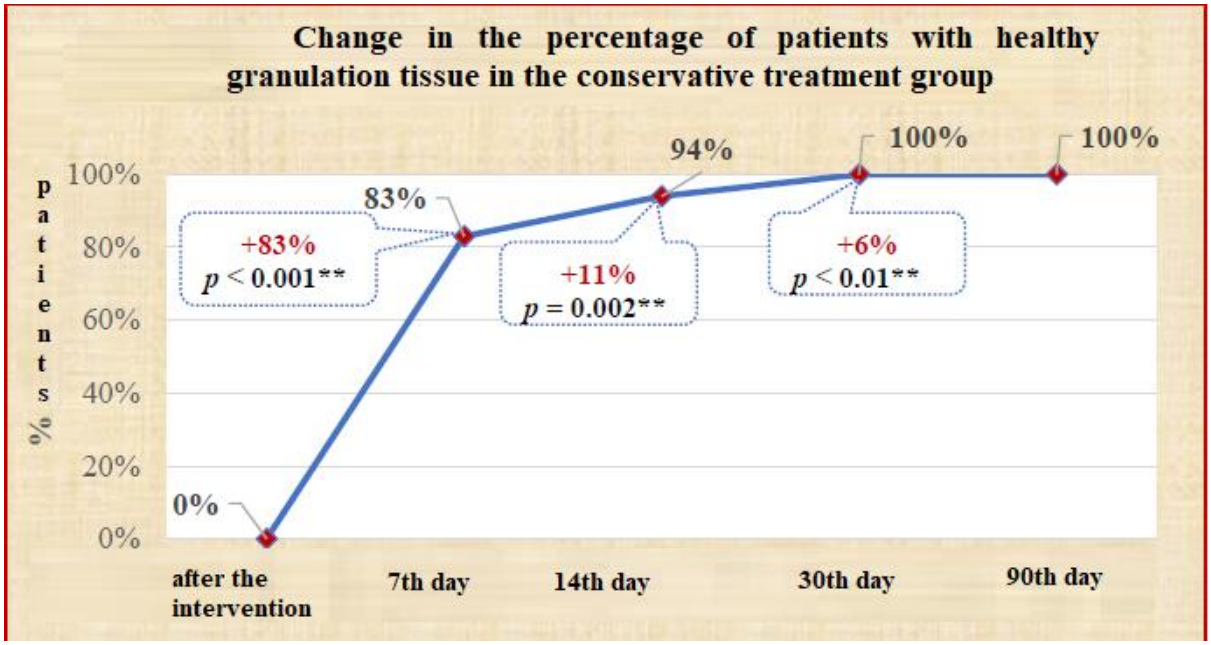


Fig. 59. Change in the percentage of patients with healthy granulation tissue in the conservative treatment group

Presence of signs of epithelialization

Signs of epithelialization are not detected immediately after the intervention, regardless of the type of treatment. On the 7th day, they were observed in 80% of the PRF group and in 43% of the conservative treatment group, with a significant difference of 37%, $p < 0.001$. On the 14th day, 100% of patients on PRF treatment showed signs of epithelialization, whereas in conservative treatment signs were reported in 55%, with a significant difference of 45%, $p < 0.001$. On the 30th day, the percentage remained in patients on PRF treatment and rose to 63% in those on conservative treatment. The difference between the groups was 37% and was significant, $p < 0.001$. A similar trend is reported on the 90th day. Although in the conservative treatment group, the percentage increased to 87%, the difference with the PRF group remained significant, $p = 0.001$.

Tracking of signs of epithelialization	Type of treatment		Fisher's test	
	PRF	Conservative	difference	p
After treatment	0 0%	0 0%	0%	-
7th day	47 (80%)	*76* (43%)	37%	.000**
14th day	59 (100%)	98 (55%)	45%	.000**
30th day	59 (100%)	113 (63%)	37%	.000**
90th day	59 (100%)	154 (87%)	23%	.001**

** Statistical significance at p <0.05; ** Statistical significance at p ≤ 0.01*

The change in signs of epithelialization for the five time points in the group of patients treated with PRF was illustrated in Fig. 60. No epithelialization was observed in any of the patients immediately after the intervention. On the 7th day, epithelialization was found in 80% of PRF patients and the percentage increase was significant, p <0.001. On the 14th day, 100% of patients showed signs of epithelialization, with a significant increase of 20%, p <0.001. On the 30th and 90th day, signs of epithelialization persisted in 100% of patients undergoing PRF treatment.

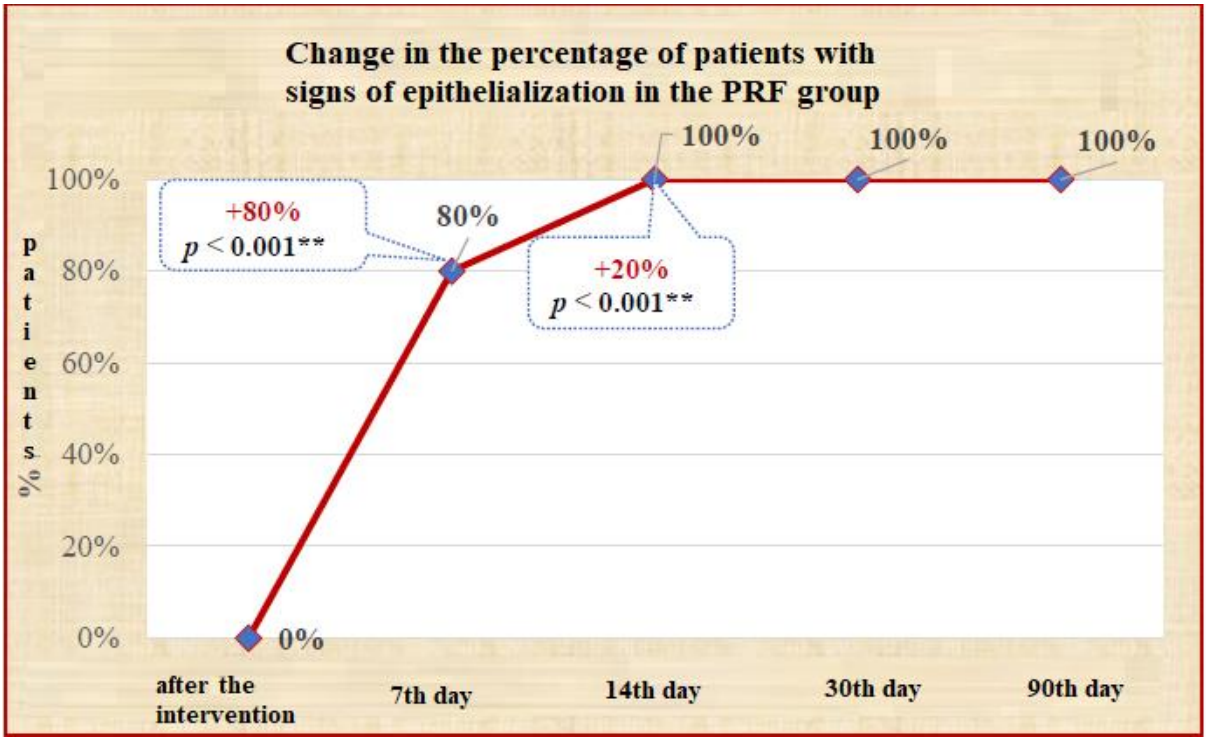


Fig. 60. Change in the percentage of patients with signs of epithelialization in the PRF group

The change in signs of epithelialization for the five time points in the group of patients undergoing PRF treatment is illustrated in Fig. 61. Immediately after the intervention, epithelialization was not observed in any of the patients. On the 7th day, epithelialization was found in 80% of PRF patients and the percentage increase was significant, p < 0.001. On the 14th day, 100% of patients showed signs of epithelialization, with a significant increase of 20% compared to day 14, p < 0.001. On 30th and 90th day, signs of epithelialization persisted in 100% of patients receiving PRF treatment.

Conservative treatment also showed an increase in the percentage of patients with epithelialization, but not as sharply as with PRF treatment. On the 7th day, 43% of patients showed signs compared to 0% immediately after the intervention. The increase is significant, p < 0.001. On the 14th day, a new significant increase of 12% occurred and a total of 55% of patients showed signs of epithelialization, p = 0.026. On day 30, 63% of patients showed stubborn signs, but the increase of 6% was not significant, p = 0.131. On the 90th day, a

significant increase of 24% occurred and patients with symptoms accounted for 87%, $p < 0.001$. It should be noted that in this group 100% of the presence of signs of epithelialization is not reported. At the end of time, 13% of patients did not show such signs.

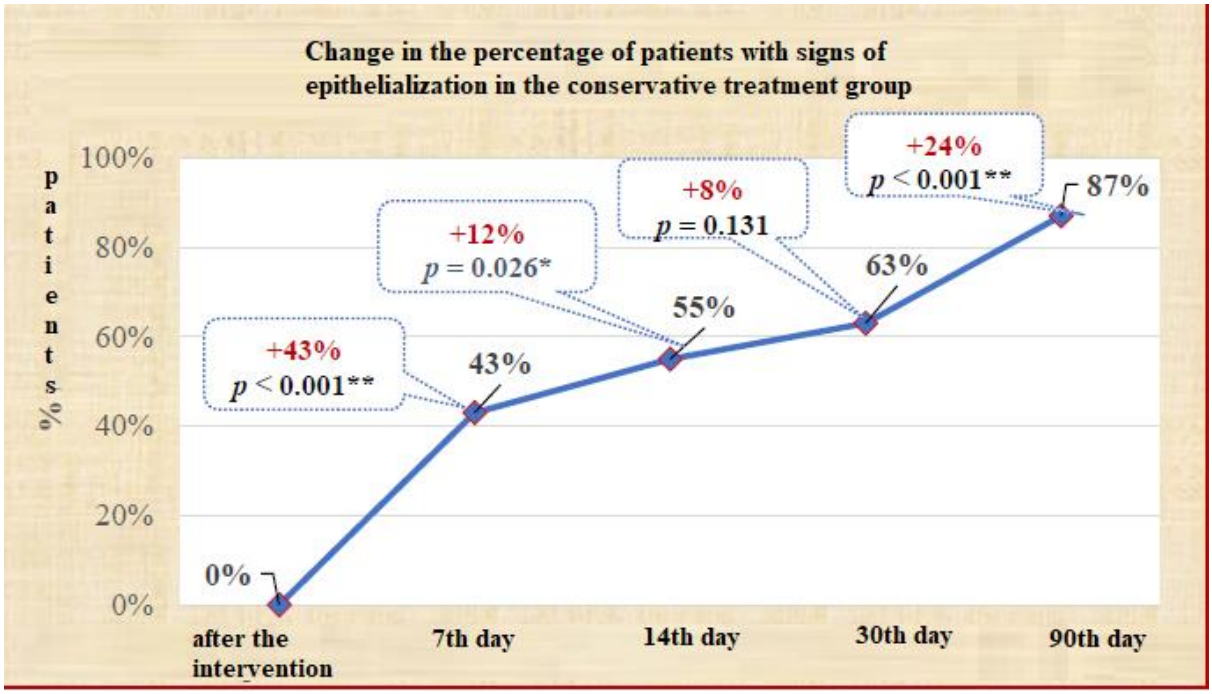


Fig. 61. Change in the percentage of patients with signs of epithelialization in the conservative treatment group

Summary of the results to the fourth task

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.

IV. SUMMARY AND CONCLUSIONS

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.
3. PRF treatment shows much better results in terms of bone density, bundle and lingual width than conservative treatment and in the long run. Over time, it has significantly higher values in the group treated with PRF, where 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. The buccal width in the PRF group decreased on the 90th day compared to the conservative treatment group. 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 and 90th day, and in conservative treatment there was an increase between the two time points.
4. No statistically significant differences were found in the anatomical and topographic localization of the 6th month in the two types of treatment. There are some differences in size. With PRF treatment, a higher percentage of patients with a size of ≤ 1 mm was observed. The majority of the PRF group are in the first two size categories: ≤ 1mm and> 1 - 3mm. The majority of patients on conservative treatment are > 1 - 3 mm and > 3 - 5 mm in size.
5. PRF treatment showed much better overall long-term results in follow-up with 6-month computed tomography compared to conservative treatment. PRF treatment is characterized by a significantly higher percentage of patients with strong shadow intensity, while conservative treatment is dominated by a percentage with low intensity.

6. Comparing the two types of treatment in terms of homogeneity and contours, patients treated with PRF have significantly better results at 6 months. In PRF treatment dominate homogeneity and sequestration, while in conservative treatment this process is slower. The presence of inhomogeneity is also established. In patients on PRF treatment, sharp and continuous outlines predominate, while in patients on conservative treatment, blurred and interrupted outlines are more common.
7. None of the patients in the PRF treatment group showed a change in the surrounding bone, in contrast to the conservative treatment group.
8. PRF treatment shows good results in terms of healing: healthy granulation tissue appears on the 7th day; the development of signs of epithelialization in the PRF group was rapid and by the 14^{th} day all patients showed signs of epithelialization. In the conservative group it is slower and more gradual and does not reach 100%.
9. Treatment of MRONJ with a platelet-rich fibrin membrane shows reliable results in both short and long term in terms of healing of both soft and hard tissues. It shows much better results in epithelialization and bone density, as well as overall healing, compared to conservative treatment. It could be used as a modern alternative to drug treatment.

V. CONTRIBUTIONS

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 autir 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.