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APPLICATION OF PLATELET-RICH FIBRIN AS A METHOD OF TREATMENT FOR MEDICATION-RELATED OSTEONECROSIS OF THE JAWS IN BULGARIA

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Abstract

Lately, medication-related osteonecrosis of the jaw (MRONJ) has emerged as a common disease due to the increasing use of antiresorptive drugs (intravenous bisphosphonates) for the treatment of oncological and osteoporotic diseases, which at an advanced stage significantly affects the quality of life of patients.

Therefore, new therapies that accelerate the recovery of musculoskeletal tissue have become preferred in the treatment of such diseases in recent years.

An innovative approach, which supports the healing processes is the application of autologous platelet concentrates known as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF).

Platelets are unique blood elements responsible for hemostasis. Activated platelets secrete a large amount of growth factors that initiate regeneration in soft tissues and bones.

PRP is plasma with many more platelets than are usually found in the blood. The concentration of platelets and therefore the concentration of growth factors may be 5–10 times higher (or richer) than usual.

PRF is a biological material, which has the ability to release growth factors over time. Growth factors stimulate stem cells, which improve collagen and elastin in the skin. Platelets in PRF are thought to survive better than those in PRP and thus contribute to faster recovery and formation of new tissue.

Fibrin is a biological scaffold that forms when an injury occurs anywhere in the body. Platelets normally circulate in the blood and bind to the fibrin

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scaffold. Thus connected, they are activated and release growth factors, which are small "granules". These growth factors begin the process of wound healing by creating new skin cells, collagen and blood vessels.

The present study is related to the treatment of MRONJ with PRF. It is aimed at researching the attitudes of oral and maxillofacial surgeons in Bulgaria regarding the application of innovative medical technology such as PRF in the treatment of MRONJ. An author's questionnaire was developed with the help of which the survey was carried out.

The analysis of the data shows that the interest in PRF in Bulgaria is great, but unfortunately it is rarely applied. However, respondents believe that this is a promising and innovative method in various aspects of surgery.

Key words: growth factors, platelet rich fibrin, platelet rich plasma, wound healing, bone regeneration

Introduction. The drug-induced osteonecrosis of the jaws was first described in 2003 by Marx [1]. It is triggered by medications that belong to the group of bisphosphonates and/or monoclonal antibodies. These medications block osteoclast activity and thereby stop bone resorption. They are used to treat bone metastases – most often breast cancer and prostate cancer, as well as multiple myeloma and osteoporosis.

The presence of necrotic bone that is open and despite treatment has not healed for 56 days (about 8 weeks) is defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS)[1] as medical osteonecrosis of the jaws.

Once started, medicated osteonecrosis is difficult to treat. Frequently, the methods of treatment are conservative – the use of antibiotics and local antiseptics, physiotherapy and surgical – removal of necrosis.

Regenerative medicine focuses much of the research on the study of intercellular communication and intracellular transduction of signalling proteins. They affect the behaviour of the cell phenotype (autocrine) or the behaviour of other neighbouring cells (paracrine) by interacting with specific transmembrane receptors located in the cell membrane.

The results of these studies will lead to more innovative therapies for faster and more efficient tissue regeneration.

Over the last decade, the development of platelet-rich plasma (PRP) technology has emerged.

PRP is generally described as a non-operative procedure for cartilage injuries [2].

The main reason for its use are its functional components. Megakaryocytes produce platelets as annuclear cells [3]. They entail different factors, such as growth and coagulation, as well as chemokines, cytokines, integrins and adhesion [4]. When the platelets in PRP are activated they can secrete growth factors,

[1] https://www.aaoms.org/docs/govt_affairs/advocacy_white_papers/mronj_position_paper.pdf

which are many times greater than the ones that are at baseline in the blood. These platelets have assumed the role of mediators and modulators in case of an inflammation. The plasma proteins incorporated in PRP are crucial components in the healing process of connective tissue stroma [5].

PRP therapy is firmly entrenched in the clinical practice of various fields of medicine [6–9]. This method occupies a leading position in the field of cosmetology and aesthetic medicine, allowing to compensate for age-related skin changes, providing a powerful proregenerative effect [10].

Historically, the application of PRP began in regenerative medicine in the 1980s. Taking advantage of the hemostatic and sealing properties of fibrin, in the late 90s PRP began to be used mainly in oral and maxillofacial medicine. Following the first description of an ambulatory method for obtaining PRP by Anitua in 1999, various techniques and potential applications have been described.

One striking example of the proven clinical effect of PRP therapy is the stimulation of chronic wound healing [11]. Dermatologists, dentists, gynecologists, urologists, cardiac surgeons and many other specialists have successfully used PRP therapy in daily practice [7, 11, 12]. The use of cellular technologies in clinical practice requires compliance with certain requirements and conditions that ensure the safety and effectiveness of treatment [13]. Today, it has been unequivocally proven that PRP therapy is an absolutely safe method of treatment. This is due to autologous biological material that does not contain allergens and mutagens. However, the situation is not so clear about the effectiveness of PRP therapy [8]. The key factor determining the effectiveness of PRP therapy is the characteristics of the final bioproduct, or more precisely the number of platelets in the plasma after separation of blood fractions.

Methodology. This study was related to the treatment of MRONJ with RTF. It is aimed at studying the attitudes of of specialists in the field of dental medicine and surgery, in Bulgaria regarding the application of innovative medical technology such as RTF in the treatment of MRONJ. The target group of the study is composed of 131 professionals in these fields of work experience as follows: experience over five years – 48.1% ($n = 63$); experience up to five years – 35.9 % ($n = 47$); no experience or up to one year 16% ($n = 21$).

To test the working hypothesis and realize the objectives of the survey, a questionnaire survey was conducted. The questionnaire consists of 14 questions divided into two groups. The first group is related to MRONJ and its degree of manifestation in patients. The second includes questions related to the popularity and application of PRF in Bulgaria. The study involved 131 ($n = 131$) specialists from different fields of practice related to surgery.

Working hypothesis:

H1: The treatment of MRONJ with PRF is an innovation that is rare in Bulgaria.

H2: In Bulgaria, the treatment of MRONJ is carried out mainly by conservative antibiotic therapy.

H3: The treatment of MRONJ with PRF is of interest to the majority of specialists in the field.

To achieve greater credibility, the survey was conducted online through google doc forms, which guarantees the anonymity of the participants.

Results. The study shows that nearly 90% ($n = 115$) of the respondents encounter MRONJ almost daily in their practice (Fig. 1), recognize its symptoms compared to other diseases with a similar course and perform surgical treatment of pathological processes in the oral cavity and dental tissues, in patients with this diagnosis.

The specialists who perform surgical treatment of pathological processes in the oral cavity and dental tissues in patients with MRONJ 76.6% ($n = 126$) have a high relative share. Only 3.5% ($n = 5$) of the respondents do not perform such treatment due to the fact that they are young specialists.

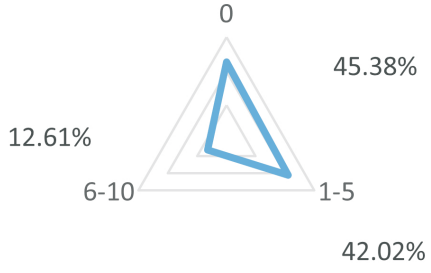

Fig. 1. Number of patients with MRONJ per month

Most of the respondents 30.5% ($n = 40$) note that the main oncological diseases in the patients with MRONJ that they observed is a Metastatic cancer that has spread from the primary site to other parts of the body (Table 1). The next common oncological disease in patients with such a diagnosis is breast cancer 22.9% ($n = 30$) and prostate cancer 21.4% ($n = 28$).

Table 1

The main oncological disease in patients with MRONJ

Cases	Percentage	Valid percentage	Cumulative percentage
I do not have such patients	3.1	3.1	3.1
Lung carcinoma	8.4	8.4	11.5
Breast carcinoma	22.9	22.9	34.4
Prostate cancer	21.4	21.4	55.7
Metastases	30.5	30.5	86.2
Other	13.8	13.8	100
Total	100	100	

The main intake of chemotherapeutics administered by the respondents was combined 51.1% ($n = 67$). Intravenous chemotherapy is used by 35.1% ($n = 45$), while oral treatment is used only in 13.7% of the cases ($n = 18$).

The dentists and oral doctors' awareness of MRONJ, as well as their willingness to work in direction of reducing the risk of this disease is of key importance. The level of knowledge in dental practice is crucial for the timely and correct referral of patients to a specialist in case of suspicion of the development of MRONJ and the application of adequate treatment. The study shows that 56.5% ($n = 74$) are interested in and familiar with the methods for diagnosing MRONJ. Only 8.4% ($n = 11$) have no information about these methods, and 35.1% ($n = 46$) have only heard of them.

The most used approach for treatment of MRONJ according to 47.5% ($n = 63$) of the respondents is excision of the tumour mass. With similar values (16.3–19.2%) are the specialists using excision and placement of PRF, curettage and tumour resection. The most common treatment of patients with MRONJ is by curettage and revision of the lesion (65.78%) ($n = 86$), by extraction – 21.4% ($n = 28$), by incision – 5.3% ($n = 7$), and 4.42% ($n = 6$) of the respondents referred the patient to an oral and maxillofacial surgeon.

Slightly more than half of the respondents 58.7% ($n = 77$) do not prepare conventional imaging or specific examinations preoperatively for patients with MRONJ, but consult an oncologist; 38.1% ($n = 50$) of the respondents do such tests. The percentage of cases in which chemotherapeutics are discontinued 3.1% ($n = 4$) is small.

Professionalism – the result of many years of experience (theoretical and practical) and the application of modern treatment techniques allow each patient to choose the most appropriate treatment behaviour – conservative or operative. The currently known recommendations for such behaviour in MRONJ after and before surgery are followed by 92.4% ($n = 121$). The percentage of participants, who apply these recommendations, but not for all of their patients is small – 7.6% ($n = 10$).

Conducting follow-up examinations after treatment is necessary to check complaints or the absence of such in the patient, visual inspection and conventional radiography, and in case of suspicion of deepening the process – computed tomography, nuclear magnetic resonance spectroscopy, scintigraphy.

Table 2 presents the main periods of control examinations performed by the respondents.

The majority of the respondents – 74.1% ($n = 97$) believe that the surgical treatment they use gives satisfactory results. The percentage of those who consider the achieved results to be good is 12.7% ($n = 16$) and those who do not have good results are around 13.2% ($n = 18$). It is noteworthy that none of the respondents observed a very good or excellent effect of the methods used so far.

The survey shows that PRF treatment is a method which is very rarely used in Bulgaria, but at the same time the practitioners show great interest in it. Respondents believe that it is promising and gives satisfactory results. Only a small percentage of respondents are not sure about its effectiveness (Table 3).

Table 2

Interval of control examinations in patients with MRONJ

Cases	Percentage	Valid percentage	Cumulative percentage
Until the 15th day	50.4	50.4	50.4
After a month	1.5	1.5	51.9
On the 3rd month	29.8	29.8	81.7
On the 6th month	8.4	8.4	90.1
After two years	3.1	3.1	93.2
Individually	3.7	3.7	96.9
I do not treat such patients	3.1	3.1	100
Total	100	100	

Table 3

Opinion on the treatment of MRONJ with PRF

Cases	Percentage	Valid percentage	Cumulative percentage
I don't treat MRONJ	3.1	3.1	3.1
I use PRF to treat another disease	1.5	1.5	4.6
The treatment gives satisfactory results	5.3	5.3	9.9
I have no experience, but the method is promising	84	84	93.9
A method with unclear effectiveness	6.1	6.1	100
Total	100	100	

Conclusion. The study proves all three hypotheses. Specialists in the field of oral and maxillofacial surgery are familiar with the possibilities of applying PRF. Many of them are even interested and follow innovations in this regard, but use traditional methods for the treatment of MRONJ. Only 5% of the respondents mention that they apply this method in their practice, which confirms the hypothesis of innovation and rarity of the method.

The large percentage of specialists interested in the approach is an indirect proof of its prospects.

A major breakthrough in the treatment of many medical conditions is represented by therapies with PRP. Due to the important consequences for our future health, this therapy is one of the hottest topics in regenerative medicine.

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