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Prevention of Complications in Patients Suffering From Pathological Mandibular Fractures Due To Bisphosphonate-Associated Osteonecroses.

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ABSTRACT

The article studies the correlation between long-term use of phosphorus-containing drugs and pathological mandibular fractures. It has been established that the development of complications is facilitated by the chemical activity of bisphosphonates that decelerates and inhibits metabolic processes in bone tissue, which is accompanied by increased bone mineralization and bone brittleness. The need for designing and manufacturing an apparatus that can mimic the anatomical integrity of the mandible, ensuring its functional activity in patients suffering from pathological fractures due to the bisphosphonate-associated osteonecrosis, has been substantiated.

Keywords: mandibular fracture, bisphosphonate-associated osteonecroses, medications

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INTRODUCTION

Currently, bisphosphonates are used to treat malignant diseases; medications are administered intravenously for prevention of bone metastases and their complications [2]. Bisphosphonates are also used to treat pathological metabolic processes and osteoporosis, Paget's disease, pediatric osteogenesis imperfecta in order to prevent the unbalanced action of osteoclasts that break down the mineral structure of bone [2, 4, 12]. Recent years have seen an increase in the number of patients with osteonecroses of facial bones who are addicted to desomorphine and pervitin, made from red phosphorus. In recent years, there is a tendency for an increase in clandestine production of desomorphine and its use in different regions of the Russian Federation: from 16 regions in 2006 to 60 regions in 2009 [4]. In the first quarter of 2010, 150 million average single doses of desomorphine were seized, which, according to the Federal Drug Control Service of the Russian Federation, was equivalent to the annual demand of 300,000 people for desomorphine [8, 9, 10].

The most common symptom of bone metastases is pain. Mechanical factors of pain syndrome include increased intraosseous pressure, soft tissue compression and mechanical compression of bone. Chemical factors include prostaglandin E, acidosis, accompanying osteolysis and factors produced or activated by tumor [3, 5, 11, 13, 14]. In the early stages of metastasis development pain occurs due to irritation of intraosseous and periosteal nerve endings, which is caused by cytokine secretion and an elevated intraosseous calcium level.

Pathogenetic peculiarities of interaction between phosphorus, found in medications used for treatment for cancer and those used in the production of synthetic drugs, and cellular and enzymatic systems are currently not fully understood [1, 2, 6].

According to some authors, in the early stages of cancer metastasis pain is the main symptom and occurs due to irritation of intraosseous and periosteal nerve endings, which is caused by cytokine secretion and intraosseous hypercalcemia. As cancer spreads from its primary site, the pain syndrome progresses, which is also caused a number of factors. For example, the observed increase in intraosseous pressure was caused by acidosis that was caused or activated by chemical reactions in the soft tissue tumor focus, which contributes to the appearance of peripheral edema and congestion and causes mechanical compression of bone tissue [3, 7, 9, 10].

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Figure 1: Clinical manifestations of bisphosphonate-associated osteonecroses in the maxillofacial region

This pain is not related to loading on the bone and may even intensify when the bone is kept motionless. However, as bone destruction progresses, the so-called functional pain occurs due to mechanical weakening of bone structures and their instability. Functional pain increases with loading on the affected bone and may indicate a risk of pathological fracture.

Pathological fractures are preceded not only by the appearance of exposed bone in the oral cavity, prolonged soft tissue infiltration, no signs of pyesis being observed. Pathological fractures are accompanied by displacement and abnormal function due to infiltration of muscle, the secondary infection of which makes patients suffer from excruciating pain and worsens the functional impairment (Figure 1).

Taking into account the existing pathogenetic aspects of bisphosphonate-associated osteonecrosis, we determined the **research goal** that consisted in substantiating the need for designing and manufacturing an apparatus that can mimic the anatomical integrity of the mandible, ensuring its functional activity in patients suffering from pathological fractures due to the bisphosphonate-associated osteonecrosis.

TECHNIQUE

Surgical treatment was received by 15 patients who sought medical help and were under observation in the Department of Oral and Maxillofacial Surgery of the Stavropol Regional Clinical Hospital, characteristic clinical features of a pathological mandibular fracture being observed. We used the standard bidirectional Ilizarov apparatus for fixation in 12 patients. During the early postoperative period, the standard apparatus performed the function of an immobilization device, which facilitated the restoration of the functional activity of the mandible and muscular apparatus. We used the apparatus of our own design in 3 patients.

FINDINGS

Clinical observation has revealed the improvement in the patients' general condition due to a significant decrease in the phenomena related to pain syndrome. Moreover, during 12-14 days (the period during which the apparatus were in a quiescent functional state) arresting of soft tissue infiltration was observed. Suppuration was almost absent (according to the microflora test results, no pathogenic microorganisms were detected); scanty growth of granulation tissue in the mouth of the fistulous passage was observed.

However, activation of the apparatus and their dynamic loading with a view to optimizing the functional activity of the affected complex of organs, regardless of the time of the beginning of the activation process, led to instability of the fixing constructions. The clinical picture remained positive only during a limited period of time due to limited functionality of the standard apparatus that were used.

When fixation of the construction became less rigid, there was a need for repeated surgical interventions aimed at stabilizing the fixing constructions. However, in the treatment group there were three patients with bilateral pathologic fractures, and in this case repeated surgical interventions were not technically feasible because of progressive osteonecrosis and limited functionality of standard bidirectional apparatus.

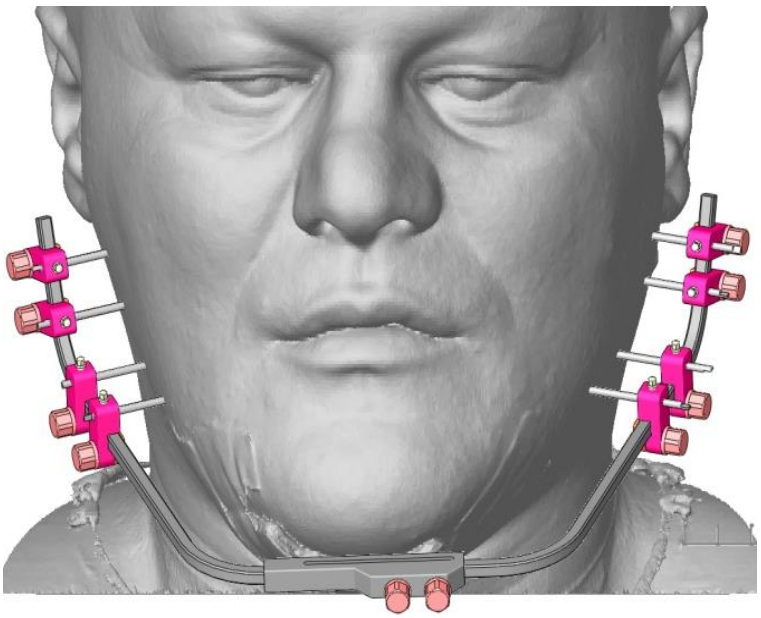
Using the results of the analysis that had been carried out and taking into account the goal and objectives of the research, we developed and proposed the method of prevention of pathological mandibular fractures and their complications by means of rigid immobilization of jaw fragments.

The following clinical case can serve as a good example. In March of 2013, V. born in 1971 sought medical help in the Department of Oral and Maxillofacial Surgery of the Stavropol Regional Clinical Hospital. He complained of the following: diffuse pain in the lower jaw, radiating along branches II of pair V of cranial nerves, mainly in the right side, unbearable, nonnarcotic analgesic drugs do not alleviate pain; general weakness; a defect in the mucosa in the oral vestibule and mandible exposure; suppuration through the fistulous passage in the submental region.

The patient had a history of use of clandestine desomorphine (1.5 years) made from medications ("Codelac", "Terpincod", "Tetralgin", "Pentalgin", "Sedal-M"). During the manufacturing process, desomorphine is treated with benzene or acetone. Moreover, it contains crystalline iodine, red phosphorus and a number of toxic substances. It has been proven that the chemical substances that desomorphine contains are able to exert local toxic and common teratogenic effects on various organs and tissues of the organism.

The patient said that the dentist had removed his lone standing, mobile lower right canine about 5 months before, without pronounced pain symptom being present. After the tooth had been extracted, the socket did not close up and after a while suppuration appeared. During five months, the patient underwent periostotomy three times; however, relief did not come. The patient said that there was catastrophically rapid bone exposure in the oral cavity after each surgical procedure.

On admission to the department, the patient underwent general examination, multidetector computed tomography with three-dimensional reconstruction was performed, the patient received a course of anti-inflammatory, neurotropic, general therapy and was discharged with improvement seven days later to be under observation of the surgeon of the local hospital, recommendations being given.



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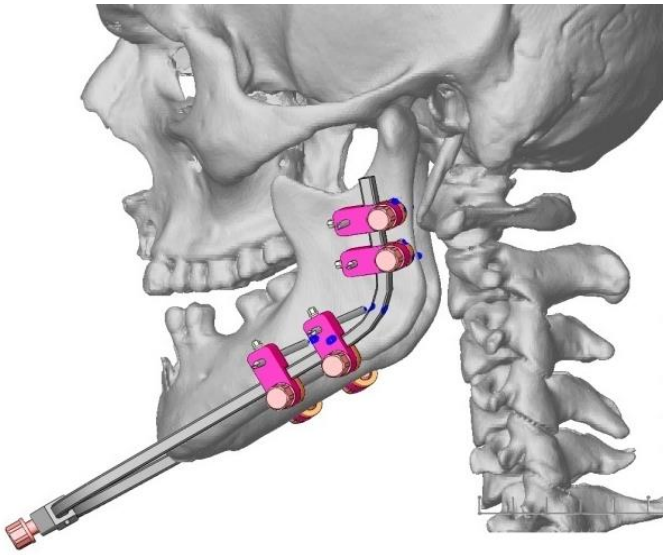

Figure 2: Use of virtual modeling for manufacturing an individual multifunctional apparatus

According to the control orthopantomogram that was performed 2 months later, the extension of the pathological process, characterized by destruction of bone tissue in the projection of the posterior teeth of the lower jaw (the right side) and the chin, was observed. Destruction of bone tissue in the projection of the mandibular body (the right side) was observed, the integrity of the compact layer of the mandibular body being preserved within the area of up to 5 millimeters.

We took into account the negative outcome of treatment of 12 patients with the help of standard apparatus and the clinical and radiographic picture of patient V. in order for an individual multifunctional apparatus to be manufactured for prophylactic and therapeutic purposes with due regard for the data obtained with the help of virtual modeling (Figure 2).

Mounting and fixation of the apparatus was performed as a planned procedure under endotracheal anesthesia, the pronounced pain syndrome being taken into account. During the mounting of the apparatus, the functional activity of some of its individual components was evaluated (Figure 3).

Figure 3: Patient V. after surgery

In the course of surgery, the anatomical jaw relationship and normal occlusion were preserved. In the early postoperative period, the patient noted improvement in his general condition, reduction in suppuration and significant reduction in the pain syndrome. The removal of the necrotic bone that had been performed contributed to arresting the local clinical symptoms of inflammation within a short time (Figure 4). The bone

biopsy in 5 patients who were under observation revealed pronounced deceleration of bone metabolism and significant deceleration or, in some cases, complete inhibition of the healing process. It was also revealed that 37% of the patients who took clandestine bisphosphonates and 63% of the patients took officinal drugs.

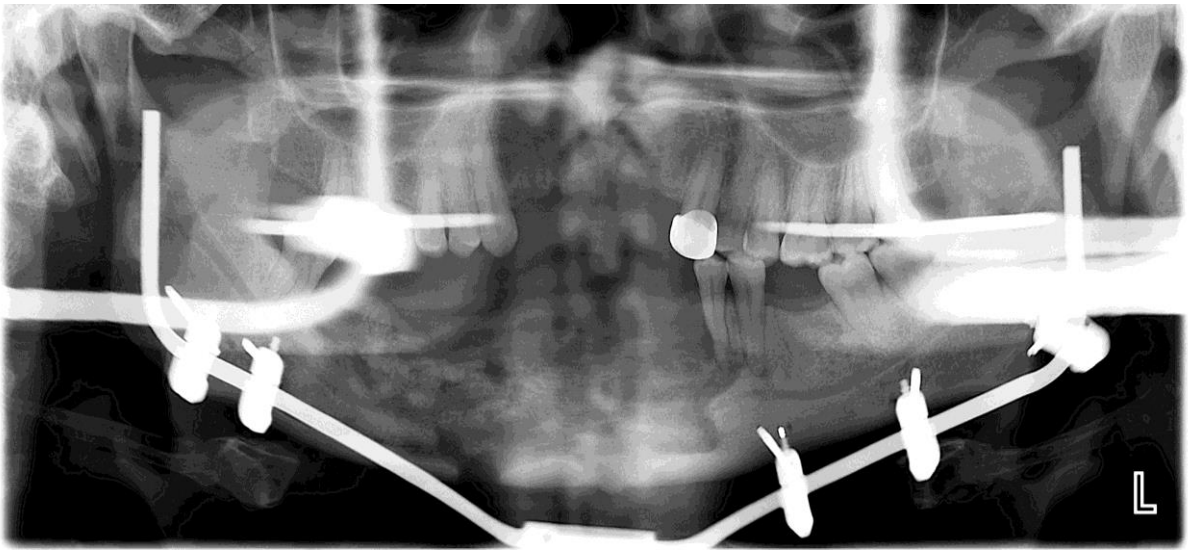

Figure 4: Patient V.'s orthopantomogram

The fractures in the patients who had been taking bisphosphonates for a long time (4.3±0.8 years) had specific radiographic features that manifested themselves in diffuse bone lesions and thinning of the cortical layer accompanied by fractures and infiltration of the surrounding tissues. Such features were not observed in the patients who had been taking bisphosphonates for a shorter period of time (1.5±0.3 years). In the group of patients who took bisphosphonates for medical reasons, oral cavity sanitation revealed that destructive and inflammatory phenomena were minimal, but there were phenomena in the patients in this group with hygienic levels below 0.5 U that are characteristic of a widespread inflammatory process.

CONCLUSION

Overall, the available literature data and the obtained clinical and radiographic data confirm a close correlation between long-term use of phosphorus-containing drugs and development of pathological fractures and their complications. It is obvious that that the development of complications is facilitated by the chemical activity of bisphosphonates that decelerates and inhibits metabolic processes in bone tissue, which is accompanied by increased bone mineralization and, as a consequence, bone brittleness. Timely prevention of these complications is needed, that is why the manufacturers should add the following information to data sheets for bisphosphonates: the following recommendations should be included in the section "Warnings and precautions": X-ray examination of facial bones on a regular basis (at least once in three months), mandatory X-ray examination of jaw bones of people who take synthetic drugs in addition to examination for detecting dangerous infection; in the section "Possible adverse reactions or side effects" there should be information about the risk of pathological fractures, possible pre-fracture symptoms (idiopathic toothache, pain in the thigh, general weakness and discomfort) should be listed.

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