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Geovana Esteves Marques

OSTEONECROSE DOS MAXILARES ASSOCIADA A MEDICAMENTOS: uma revisão de literatura

Palmas – TO

2022

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Projeto de Pesquisa elaborado e apresentado como requisito parcial para aprovação na disciplina de Trabalho de Conclusão de Curso (TCC) II do curso de bacharelado em Odontologia do Centro Universitário Luterano de Palmas (CEULP/ULBRA).

Orientador: Prof. Me. Igor Fonseca dos Santos

Linha de pesquisa: Abordagens preventivas e terapêuticas em Odontologia.

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Aprovado em:_____/_____/_____

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Centro Universitário Luterano de Palmas – CEULP

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2022

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“É preciso suportar duas ou três larvas se quiser conhecer as borboletas”.

Antoine de Saint-Exupéry

SUMÁRIO

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Review

Medication-Related Osteonecrosis of the Jaw: A Literature Review

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Abstract

Medication-related osteonecrosis of the jaw is a recent pathology, initially mentioned in 2003 by Marx, but associated only with the bisphosphonates. In 2011, other studies showed that drugs from other groups of medication were also responsible for developing the disease. Currently, antiresorptive and angiogenic drugs are correlated as risk factors for osteonecrosis of the jaws, but there are other risk factors, such as smoking, alcohol intake, drug use for more than three years, obesity, treatments with use of corticosteroids and chemotherapy drugs. The associated local factors are linked to surgical procedures such as extractions and dental implants, due to the inflammatory process generated at the spot. The disease has several stages, and may be symptomatic or asymptomatic, depending on the stages. In its clinical characteristics, it can demonstrate the presence of necrotic bone exposed in the oral cavity with or without the presence of intraoral or extraoral fistula. Treatment consists of proservation and postponing surgical procedures as much as possible, with endodontic or periodontal treatment being the best conduct. Methodology: the present study qualifies as a literature review having the "Pubmed" database as a source of bibliographic research, using keywords such as "MRONJ", "Osteonecrosis", "Antiresorptive", "Antiangiogenic", among others. It was concluded that there are few studies on this topic, but currently studies point to two groups of drugs as risk factors for the development of the disease, in addition to local and systemic factors.

Keywords: Antiangiogenic, Antiresorptives, Biphosphonates, Osteonecrosis

INTRODUCTION

Osteonecrosis of the jaws is a pathology that can be defined as the presence of non-vital bone tissue due to discontinuity of blood supply, thus causing the death of cells present at the site and degeneration of organic matrix (Bast et al., 2013). The American Association of Oral and Maxillofacial Dental Surgeons (AAOMS) declares that to be considered medication-related osteonecrosis of the jaw, under the acronym "MRONJ", it is necessary that the patient has undergone:1. previous or ongoing treatment with antiresorptives, whether or not it is accompanied by immunomodulators or anti-angiogenic drugs; 2. bone exposed or capable of being probed by a fistula, whether intraoral or extraoral in the maxillofacial complex that is more than 8 weeks old; and3. no previous history of radiotherapy or metastatic pathologies in the head and neck region. (Ruggiero et al., 2022).

Kün-Darbois and Fauvel in their study point out that

one of the causes of this decrease in blood supply is the use of antiresorptive drugs (Bast et al., 2013; Ruggiero et al., 2022). According to Neville, these drugs have many benefits for people being treated for metastatic carcinomas, hypercalcemia and osteoporosis, but they have serious adverse effects, such as the development of this pathology. Initially, this disease was called bisphosphonate-associated osteonecrosis of the jaw (BRONJ), but later, drugs were observed that are not included in this group and that can develop the pathology, being now called medication-related osteonecrosis of the jaw (MRONJ) (Neville et al., 2016).

Drugs outside the bisphosphonate group have shown a relationship with the development of the disease, due to their action on osteoclastic cells (Hasegawa et al., 2021). These drugs belong to the class of angiogenesis inhibitors and anti-kappa-B nuclear factor activating receptor (denosumab), reported Kawahara (Kuroshima et al., 2019; Kawahara et al., 2021).

But in addition, other factors can contribute to this picture. The AAOMS points out in its research that there is a strong relationship between MRONJ and the inflammatory process, often caused by surgical procedures in dentistry, such as tooth extractions. However, it emphasizes that the pathology does not develop without the association of any of these drugs (Ruggiero et al., 2022). The present study aims to identify which drugs are related to the development of the pathology.

METHODOLOGY

The following study is characterized as a literature review with qualitative analysis, having as support for the bibliographic survey articles taken from the Pubmed database. The keywords used in the search in these databases were “Biphosphonates”, “Osteonecrosis”, “Antiresoprtives”, “Antiangiogenic”, “ONJ” and “MRONJ”. To perform the search, the keywords were used together with the Boolean operator “AND” between them and selecting the filter of publications from the last ten years.

From the methodology used, an initial sample was obtained, having as inclusion criteria, evaluation of articles with title and abstract that suited the theme proposed by the research, clarity in methodology, articles in English and Portuguese and availability of the full text, resulting in a total of 22 articles, in addition to 2 books as a source of concepts on the subject.

After reading and interpreting all the articles, some were included, and others excluded because they did not fit the topic in question. Part of these were used in the theoretical framework and from them indispensable and relevant authors were selected on the proposed topic that were included in the references of the primary research articles, and these extra works were downloaded, read and added as a secondary research source.

RESULTS AND DISCUSSION

Etiology

According to Bast, osteonecrosis can be defined as the presence of non-vital bone tissues due to the continuity of the organic tissue of the biological tissue, causing the death of cells in the organic region of the tissue. Complications may occur from treatments with radiotherapy or chemotherapy for the use of some types of drugs (Bast et al., 2013).

Osteonecrosis of the jaws is a pathology that affects the bone tissue of the maxilla and mandible causing death of the cells at the site. It is considered rare, but complex and most often affects the mandibular bone. Neville states that the mandibular bone was involved in 65% of cases, while the jawbone was involved in only 27%. It also states that in 8% of the cases both jaws were involved (Neville et al., 2016; Eguia et al., 2020).

Clinical and radiographic characteristics

American Association of Oral and Maxillofacial Dental Surgeons (AAOMS) reports that the pathology can be asymptomatic or symptomatic and can be classified into stages. In stage 0, it was presented as a loss of dental elements without odontogenic cause, without bone exposure, but may have the presence of intraoral or extraoral fistula. It can also manifest severe pain at the site, being possible to spread to the temporomandibular joint (TMJ) region, sensorineural alteration of the site and pain in the maxillary sinus region, being capable of manifesting wall thickening (Ruggiero et al., 2022).

At stage 0, radiographically, it presents as loss of alveolar bone unrelated to chronic periodontal disease, adulterated bone trabeculae, absence of evidence of bone neoformation in post-extraction sockets, area of osteosclerosis encompassing basal and/or alveolar bone and thickening or darkening. of the periodontal ligament (Ruggiero et al., 2022).

When advancing to stage 1, the characteristics are defined as necrotic bone tissue already exposed in the oral cavity and/or with the presence of a fistula that, when probed, its tracking points to the location of this tissue, without evidence of an inflammatory or infectious process, without symptomatology. Radiographic examinations demonstrate the same findings as in stage 0 (Ruggiero et al., 2022).

In the case of stage 2, the evidence points to the existence of necrotic bone tissue in the oral cavity with a fistula that, when tracking, indicates this tissue, with evidence of an inflammatory and/or infectious process, with symptoms, with radiographic findings similar to those ofstage 0 patients (Ruggiero et al., 2022).

The last stage, number 3, is characterized as non-vital bone tissue exposed in the oral cavity with the existence

of a fistula that, when traced, indicates this tissue, presenting infection. There is a possibility of one or more of these attributes: (1) non-vital bone tissue with exposure that affects, in addition to the alveolar bone area, structures such as the lower border and ramus of the mandible, maxillary sinus and zygomatic process of the maxilla; (2) evidence of extraoral fistula; (3) fractures due to pathology; (4) existence of oral communication; (5) appearance of osteolysis extending to the lower edge of the mandible or maxillary sinus floor (Ruggiero et al., 2022).

Causes

In 2003, the cause of osteonecrosis of the jaws was associated by Marx with the use of a group of drugs, the bisphosphonates. According to Neville, these drugs have many benefits for the treatment of various diseases, but they have serious adverse effects, one of which is the emergence of this pathology (Neville et al., 2016; Marx, 2003).

Neville states that these medications are used to treat several pathologies, some of which are: osteoporosis; hypercalcemia; malignant neoplasms, that is, those that have metastatic capabilities, such as multiple myeloma and breast and prostate carcinomas. They are still used in pathologies such as Paget's disease, rheumatoid arthritis and osteogenesis imperfecta, however it is not such a common treatment (Neville et al., 2016).

Initially, this disease was called bisphosphonate-related osteonecrosis of the jaw (BRONJ), but later, drugs were observed that are not included in this group and that can trigger the pathology, being now called drug-related osteonecrosis of the jaw (MRONJ) (Neville et al., 2016).

American Association of Oral and Maxillofacial Dental Surgeons (AAOMS) declares that to be considered MRONJ, it is necessary that the patient has undergone: (1) previous or ongoing treatment with antiresorptives, whether or not accompanied by immunomodulators or antiangiogenic drugs; (2) bone exposed or capable of being probed by a fistula, whether intraoral or extraoral in the maxillofacial complex that is more than 8 weeks old; and (3) no previous history of radiotherapy or metastatic pathologies in the head and neck region (Neville et al., 2016).

Risk factors

In addition to the use of the drugs mentioned above, other risk factors are associated. Neville reports that people of advanced age (above 65 years) have a greater chance of triggering the disease. Furthermore, some systemic diseases are linked to MRONJ, such as diabetes (Neville et al., 2016).

There are also habits that are also correlated, such as poor oral hygiene, smoking, drug use for more than 3 years and alcohol consumption, in addition to drug treatments such as corticosteroids and chemotherapy drugs (Neville et al., 2016).

Yoneda in your study complements saying that obesity is also a risk factor, in addition to pathologies such as hypoparathyroidism, osteomalacia, vitamin D deficiency, anemia and treatments such as hemodialysis (Yoneda et al., 2017).

But in addition, local factors can contribute to this picture. The AAOMS points out in its research that there is a strong relationship between MRONJ and the inflammatory process, often caused by surgical procedures in dentistry, such as tooth extractions. However, he emphasizes that the pathology does not develop without the association of some medication (Ruggiero et al., 2022).

Pichardo points out that in procedures such as dental implants, the chance of developing MRONJ is greater in patients who use antiresorptives intravenously when compared to patients who use these drugs orally (Pichardo et al., 2020).

Trigger drugs

Initial studies in 2003 showed that the drugs involved in the disease are bisphosphonates. However, drugs outside the bisphosphonate group were also involved, due to their action on osteoclastic cells and decreased blood supply. Kün-Darbois and Fauvel in their study point out that one of the causes of this decrease in blood supply is the use of antiresorptive drugs (Kün-Darbois and Fauvel, 2021; Marx, 2003).

Subsequently, other classes of drugs were described, namely, angiogenesis inhibitors and anti-kappa-B nuclear factor activating receptor (RANK-L binding inhibitors), Kawahara reported (Kawahara et al., 2021).

Antiresorptive Drugs

Bisphosphonates

Bisphosphonates are a group of antiresorptive drugs used to control the action of bone resorption cells. They are able to reduce the lifespan and function of osteoclasts, affecting bone remodeling and also inhibiting mediators of the inflammatory process, interfering with the healing of lesions in bone tissue (Andrade, 2014).

Consolaro in his study describes that bisphosphonates inhibit the recruitment of cells to the bone surface, prevent cell activity, reduce cell life collaborating in the apoptosis process and affect the exchange of minerals during the bone resorption process, that is, the activity osteoclast (Consolaro, 2014).

Structurally, they are derived from inorganic pyrophosphate (PPi). This is released as a by-product of synthetic reactions in the human body and can be found in various places in the body, such as blood and urine. Initial studies showed that PPi was able to act on hydroxyapatite, preventing calcification by binding the crystals, raising the suspicion that through it it would be possible to regulate bone resorption and remodeling (Drake et al., 2008).

Andrade adds that these drugs can remain in the bone tissue for a long period, from months to more than ten years, due to their great affinity for hydroxyapatite, an element very present in the bones of the human body, as it is the substance responsible for the support function. mechanic (Andrade, 2014).

Some of the drugs in this group are: etidronate, tiludronate, chlordronate, pamidronate, alendronate, ibandronate, risedronate and zoledronate. They have different doses, route of administration and potency, the most potent of which is zoledronate (Andrade, 2014).

RANK-L binding inhibitors

Another group of drugs that is part of antiresorptive drugs is the group of RANK-L binding inhibitors, with denosumab being the best-known drug. Basically, it is a fully human monoclonal antibody that acts by inhibiting the cytokine RANK-L, thus controlling bone remodeling. It has great affection for the cytokine. By inhibiting it, it prevents the recruitment, maturation, and action of osteoclasts, decreasing bone resorption (Hanley et al., 2012).

Antiangiogenic drugs

Antiangiogenic medications are drugs used to inhibit angiogenesis, helping in cases of malignant neoplasms, reducing the chance of metastasis. It acts on tyrosine kinase receptors, inhibiting their function. Thus, it disrupts the function of vascular endothelial growth factor (VEGF), hindering angiogenesis and thus hindering the growth of tumors installed at the site. Among the drugs in this group, lenvatinib is one of the best known (Leite et al., 2012; Lu et al., 2021).

Treatment

According to Neville, the surgical procedure should be postponed whenever possible, as evidence shows a close relationship between surgical procedures and the onset of the disease. In cases of coronary destruction, conventional endodontic treatment is an excellent option. In cases of dental elements with mobility up to grade 2, the best intervention is the splinting of the elements, being performed extractions only of elements with degree 3 mobility (Neville et al., 2016).

Sim et al. in his study, he points out a drug used for cases of osteoporosis that proved to be effective in the treatment of MRONJ, teriparatide, a human parathyroid hormone that acts on osteoblasts, inducing bone neoformation, proving to be a safe and effective alternative for the treatment of lesions (Sim et al., 2020).

Kwon adds that the use of teriparatide still has few studies, which are case studies or retrospective cases, requiring a well-controlled prospective study for this drug to be proven effective in cases of MRONJ (Kwon and Kim, 2016).

Ferneini emphasizes that the best way to prevent the onset of MRONJ is to avoid surgical procedures whenever possible (Ferneini, 2021).

Di Fede concludes by saying that the dentist has a fundamental role in preventing the disease and must be aware of the risk factors of patients pre-treatment or already undergoing treatment with these medications (Di Fede et al., 2018).

CONCLUSION

Through the present study, it was possible to conclude that three groups of drugs are related to the development of MRONJ, in addition to concluding that the best treatment is prevention through avoiding surgical interventions in patients who use these medications, in addition to a well-performed anamnesis. to assess the risk factors of that patient.

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ANEXOS

ANEXO A – Normas da revista Merit Research Journals

WRITING A SCIENTIFIC RESEARCH ARTICLE

FORMAT FOR THE PAPER

Scientific research articles provide a method for scientists to communicate with other scientists about theresults of their research. A standard format is used for these articles, in which the author presents the research in an orderly, logical manner. This doesn't necessarily reflect the order in which you did or thought about the work. This format is:

TITLE

Make your title specific enough to describe the contents of the paper, but not so technical that only specialists will understand. The title should be appropriate for the intended audience.

The title usually describes the subject matter of the article: Effect of Smoking on Academic Performance".

Sometimes a title that summarizes the results is more effective: Students Who Smoke Get Lower Grades".

AUTHORS

1. The person who did the work and wrote the paper is generally listed as the first author of a researchpaper.
2. For published articles, other people who made substantial contributions to the work are also listed as authors. Ask your mentor's permission before including his/her name as co-author.

ABSTRACT

1. An abstract, or summary, is published together with a research article, giving the reader a "preview" of what's to come. Such abstracts may also be published separately in bibliographical sources, such as Biological Abstracts. They allow other scientists to quickly scan the large scientific literature, and decide which articles they want to read in depth. The abstract should be a little less technical than the article itself; you don't want to dissuade your potential audience from reading your paper.
2. Your abstract should be one paragraph, of 100-250 words, which summarizes the purpose, methods, results and conclusions of the paper.
3. It is not easy to include all this information in just a few words. Start by writing a summary that includes whatever you think is important, and then gradually prune it down to size by removing unnecessary words, while still retaining the necessary concepts.
3. Don't use abbreviations or citations in the abstract. It should be able to stand alone without anyfootnotes.

INTRODUCTION

What question did you ask in your experiment? Why is it interesting? The introduction summarizes the relevant literature so that the reader will understand why you were interested in the question you asked. One to four paragraphs should be enough. End with a sentence explaining the specific question you asked in this experiment.

MATERIALS AND METHODS

1. How did you answer this question? There should be enough information here to allow another

scientist to repeat your experiment. Look at other papers that have been published in your field to get some idea of what is included in this section.
2. If you had a complicated protocol, it may helpful to include a diagram, table or flowchart to explain the methods you used.
3. Do not put results in this section. You may, however, include preliminary results that were used to design the main experiment that you are reporting on. ("In a preliminary study, I observed the owls for one week, and found that 73% of their locomotor activity occurred during the night, and so I conducted all subsequent experiments between 11 pm and 6 am.")
4. Mention relevant ethical considerations. If you used human subjects, did they consent to participate. If you used animals, what measures did you take to minimize pain?

RESULTS
1. This is where you present the results you've gotten. Use graphs and tables if appropriate, but also summarize your main findings in the text. Do NOT discuss the results or speculate as to why something happened; that goes in the Discussion.
2. You don't necessarily have to include all the data you've gotten during the semester. This isn't a diary.
3. Use appropriate methods of showing data. Don't try to manipulate the data to make it look like you did more than you actually did. "The drug cured 1/3 of the infected mice, another 1/3 were not affected, and the third mouse got away."

TABLES AND FIGURES
1. If you present your data in a table or figure, include a title describing what's in the table ("Enzyme activity at various temperatures", not "My results".) For figure, you should also label the x and y axes.
2. Don't use a table or graph just to be "fancy". If you can summarize the information in one sentence, then a table or graph is not necessary.

DISCUSSION
1. Highlight the most significant results, but don't just repeat what you've written in the Results section. How do these results relate to the original question? Do the data support your hypothesis? Are your results consistent with what other investigators have reported? If your results were unexpected, try to explain why. Is there another way to interpret your results? What further research would be necessary to answer thequestions raised by your results? How do your results fit into the big picture?
2. End with a one-sentence summary of your conclusion, emphasizing why it is relevant.

ACKNOWLEDGMENTS
This section is optional. You can thank those who either helped with the experiments, or made other important contributions, such as discussing the protocol, commenting on the manuscript, or buying you pizza.

REFERENCES (LITERATURE CITED)
There are several possible ways to organize this section. Here is one commonly used way:
1. In the text, cite the literature in the appropriate places:
Scarlet (1990) thought that the gene was present only in yeast, but it has since been identified in the platypus (Indigo and Mauve, 1994) and wombat (Magenta et al., 1995).
2. In the References section list citations in alphabetical order.

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