

Oral Mucositis in Pediatric Patients Submitted to Oncological Treatments: Literature Review

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Abstract: *Oral mucositis (OM) is an inflammation of the mucosa by the action of chemotherapy drugs or ionizing radiation, this is due to the fact that these treatment methods have deleterious effects on the oral mucosa, salivary glands, teeth, bones and masticatory muscles; is one of the most common adverse effects and represents one of the worst complications caused by antineoplastic treatment in the stomatognathic system, which when in a higher stage and with intense pain, can cause other serious complications such as malnutrition, infections and even interruption of treatment. Risk factors for this condition and its course vary depending on the type of treatment, age, sex, oral health, alcohol and tobacco use, comorbidities, and others. Pediatric patients belong to the most affected group and the main symptoms involve severe pain, xerostomia, hyposalivation, dysgeusia and dysphagia, radiation caries, trismus, dental anomalies, osteoradionecrosis are other long-term effects. For these reasons, the importance of the dentist in monitoring these patients is emphasized, performing a critical analysis of a multidisciplinary approach, from diagnosis, preventive, and corrective treatment of lesions, to offering better living conditions.*

Keywords: Oral Mucositis. Oral Cavity. Pediatrics. Oncology. Chemotherapy. Radiotherapy

1. Introduction

According to the National Cancer Institute (INCA), childhood cancer (CIJ) refers to a group of diseases that have in common the uncontrolled proliferation of abnormal cells in different parts of the body. Tumors in children and adolescents are mostly embryonic in nature, consisting of undifferentiated cells, which, in general, provide a better response to current treatments (BRASIL, 2021).

In Brazil, as well as in developed countries, statistics reveal that cancer represents about 8% of the total causes of death by disease among children and adolescents aged one to 19 years. Childhood cancer, for the most part, affects blood system cells and their supporting tissues, the most frequent types being leukemia, central nervous system brain tumors, neuroblastoma, Wilms tumor, among others (BRASIL, 2021).

For Kusuke et al. (2018), on average 40% of patients undergoing chemotherapy treatment develop side effects in the oral cavity, and this number rises to 90% when it comes to children up to 12 years of age. This is due to chemotherapy not being able to differentiate neoplastic cells from normal ones.

Oral complications of chemotherapy are related to those resulting from direct stomatotoxicity (direct action of the drug on oral tissues) that can cause xerostomia, neurotoxicity, and oral mucositis (OM), and indirect stomatotoxicity (secondary modification of tissue, such as the bone marrow). bone, increasing the risks of bacterial, viral, fungal infections, and bleeding from the oral cavity due to thrombocytopenia) (PIROLA et al., 2021).

Menezes et al. (2014) describe that mucositis is the inflammation of the oral mucosa that has as its main cause treatment with ionizing radiation and chemotherapy, being one of the most significant side effects. The onset and progression of the disease have several associated factors such as type of medication, dose, administration schedule, quality of oral hygiene, patient age, hematological changes,

sex, body mass index, changes in salivary production (PIRES et al., 2020).

This literature review aims to describe the oral health conditions of pediatric patients undergoing cancer treatment, especially OM, pointing out the clinical and therapeutic variations and the importance of the multidisciplinary team in proportion to a better quality of life for this group of patients.

2. Methodology

The present study consists of a literature review of a qualitative nature, which aims to present the oral health conditions of children undergoing cancer treatment, focusing on oral mucositis, its main clinical manifestations, and forms of treatment. The articles were selected according to systematic scientific search strategies. The journals were searched in three databases-SciELO, PubMed and Google Scholar. Articles written in Portuguese and English, published between 2007 and 2021 were selected. Free terms were used in conjunction with Boolean operators “and” and “or”, allowing a greater number of references within the pre-established criteria. The terms “oral mucositis”, “children”, “cancer treatment”, “cancer”, “chemotherapy”, “radiotherapy”, “oral health” were combined with the associations and outcomes of interest. All articles indexed between January 1, 2007, and December 31, 2021, with an experimental or observational design, were included. In addition to eliminating articles that do not comply with the aforementioned parameters, other exclusion criteria were articles not available in the free full text format, duplicate references within the databases and studies that did not match the theme in question. The studies were critically read and synthesized, evaluating the level of evidence and quality of the study, as well as its methodology, objectives, authorship aspects and others. These articles were then gathered and organized to facilitate textual understanding and statistical analysis.

3. Literature Review

The Pan American Health Organization (PAHO) states that according to the database of the International Agency for Research on Cancer (IARC), the incidence of cancer cases is intensifying over the years. It is estimated that, annually, about 400,000 children and adolescents between zero and 19 years of age are diagnosed with the disease, with leukemias, brain cancers, lymphomas and solid tumors being the most common types (ONCOGUIA, 2021).

Childhood cancer refers to a group of diseases that have uncontrolled proliferation of abnormal cells that can occur anywhere in the body. Childhood cancer (children and adolescents aged one to 19 years) corresponds to about 1% to 3% of all malignant tumors, which is considered rare when compared to adult tumors. Among the signs and symptoms, there is an abdominal mass, persistent lymphadenopathy, neurological deficit, proptosis, and white pupillary reflex, for example (LIMA, 2018).

Childhood malignancies mainly affect the cells of the hematopoietic system and supporting tissues, due to their predominance of embryonic nature, originating from undifferentiated cells, unlike adult cancer, which normally affects epithelial cells. Generally, CIJ is more aggressive and progressive within the body, in a short period, on the other hand, the response to treatment tends to be better, configuring a better prognosis (HANNA et al., 2017).

For Fermo et al. (2014), with the increase in research to approach the treatment of childhood cancer, the expectation of cure and patient survival also increased. Early diagnosis is one of the predictors of good prognosis, as well as treatment, with an average of 80% success. But when a child is diagnosed with cancer, a series of factors and impacts for the family can be seen, since there is a need for special attention and care, often changing family dynamics (SALES et al., 2012).

According to INCA, cancer treatment consists of three main modalities, they are chemotherapy (CT), surgery and radiotherapy (RT), which, due to their complexity, must be applied in a rational and individualized way. Treatment coordinated by a team of specialists from the most varied areas of health is crucial for therapeutic success, as the treatment can have consequences and side effects (BRASIL, 2021).

Among the adverse effects of radiotherapy and chemotherapy, diseases with oral manifestations are mentioned, since the oral cavity is, according to Hespanhol et al. (2010), a common site for mucositis and other complications that can be aggravated because of immunosuppression of patients, being essential to follow up with a dentist to adapt the oral environment to follow-up oncological treatment. Among the diseases triggered in the oral cavity after the start of cancer treatment are xerostomia, dental infections, gingival hemorrhages, trismus, dysgeusia, changes in the periodontal ligament, radiation caries, osteoradionecrosis, and oral mucositis.

Oral mucositis is one of the worst and most frequent complications caused by antineoplastic treatment in the stomatognathic system (SS) and results in a chain of biological events that arise in the submucosa and may progress towards the epithelium. Characterized by changes in the mucosa lining the oral cavity, this mucosal damage secondary to antineoplastic treatment triggers cellular and molecular events not only in the epithelium, but also in the underlying stroma. In addition to the direct effects of these neoplastic agents, patient age, poor oral hygiene, poor salivary function, alcohol and/or tobacco use, for example, are also risk factors (SASADA et al., 2013). The diagnosis is based on clinical manifestations, making it necessary to establish a correct differential diagnosis with other pathologies, as it is a site often associated with secondary infections of bacteria, viruses, and fungi (RODRÍGUEZ-CABALLERO et al., 2012). It is a complex biological process that comprises five phases: initiation, signaling, amplification, ulceration, and healing. There are several classifications used to grade the severity of mucositis, according to the World Health Organization (WHO) apud Santos et al. (2009), the Oral Toxicity Scale ranges from grade 0 to 4, which indicate, respectively, no change; irritation, pain, and erythema; erythema and ulcers, you can eat solids; ulcers, exclusively liquid diet; power is not possible.

Chemotherapy-associated mucositis involves the non-keratinized surfaces of the buccal mucosa, ventrolateral tongue, soft palate, and floor of the mouth. RT-induced OM affects almost all patients undergoing radiation in the head and neck region, since RT mainly affects the direct mucosa of the radiation focus. The association between the two oncological therapies (chemotherapy and radiotherapy), confer an important impact on the oral mucosa, almost 90% of patients who received both treatment modalities, report mucositis (VOLPATO et al., 2007).

QT-induced OM occurs by two distinct mechanisms: direct toxicity of QT on the mucosa and myelosuppression generated by the treatment. Decreased cell turnover in the basal layers of the epithelium, which becomes unable to adequately replenish squamous cells, describes the pathogenic process. This interference in maintaining the thickness of the oral mucosa results in inflammation, atrophy, and ulcers, which can be diffuse or localized. CT also modifies the microbial flora of the oral cavity, as well as the characteristics of saliva and epithelial maturation, compromising the mucosal barrier, which, in turn, represents a greater risk factor for morbidity and mortality in these immunosuppressed patients (SASADA; MUNERATO; GREGIANIN, 2013).

The presence of a whitish color in the mucosa is one of the earliest manifestations, this is due to the absence of sufficient keratin desquamation, which is followed by an atrophy in the mucosa, edema, erythema, ulcers that can evolve with the formation of a superficial membrane. yellowish and removable fibrinopurulent, reduced salivary flow, salivary pH alteration, in addition to intense pain, burning and discomfort (NEVILLE et al., 2009).

The clinical and dental evaluation of a child with cancer begins with the analysis of the patient's general conditions and must involve the evaluation of the oral cavity throughout the process, identifying aspects and factors for the development of mucositis, to initiate a preventive and corrective of lesions, to obtain greater control of complications related to radio and chemotherapy oncological treatments (SASADA; MUNERATO; GREGIANIN, 2013).

Currently, one of the most explored methods in the area is precisely the control of OM, to offer better living conditions to patients undergoing anticancer treatment, with a preventive protocol, since the treatment is still palliative. It is necessary, a priori, patient orientation and health promotion, in relation to oral hygiene, use of dental floss, good brushing of teeth or dental prostheses (total or partial removable); in the case of patients undergoing chemotherapy and/or RT in the head and neck region, the use of fixed orthodontic appliances should be checked, which must be removed before starting treatment; verify the use of metallic restorations, which can cause back-mirror and damage the adjacent mucosa. In the case of patients with severe pain, it is recommended that brushing be performed with the finger wrapped in gauze soaked in 3% bicarbonate water or 0.9% saline solution; Mouthwashes with chamomile tea solutions, 0.12% chlorhexidine digluconate, 0.9% saline solution, 3% bicarbonate water and nystatin can also be used to prevent OM (CONJUNSKI, 2021). Once installed, the treatment of mucositis is palliative and symptomatic, based on the use of topical anesthetics, anti-inflammatory, and antimicrobial agents (RUBENSTEIN et al. apud SASADA; MUNERATO; GREGIANIN, 2013).

The low-intensity laser began to be investigated in the mid-60s, its main effects are analgesia, biostimulation and anti-inflammatory action, which comes from the emission of low-intensity radiation provided by the laser, inducing the proliferation of macrophages and increasing the population of mast cell degranulation and angiogenesis. This effect systematically precipitates healing and decreases acute inflammation, leading to rapid local repair. Associated with the use of 0.12% chlorhexidine, there may be a reduction in the severity of the disease and its side effects (KELNER; CASTRO, 2006). Low powerphotobiomodulation has been shown to aid in the healing of the oral mucosa, reducing not only inflammation, but also pain (ANTUNES et al., 2007). The use of keratinocyte growth factor (Palifermin) has shown good clinical results, it acts in inducing cell proliferation, increasing the thickness of the epithelium and reducing DNA damage, caused especially by chemotherapy (SANTOS et al., 2009). Other studies also reveal other auxiliaries for the prevention and treatment of OM, such as the use of the cytoprotective amifostine; sucralfate, which is a drug used to protect the gastric mucosa; benzydamine, a non-steroidal drug; cryotherapy, which aims to reduce the cytotoxic effect of the chemotherapeutic agent on the mucosa and the oral bioadherent gel concentrate, indicated for pain relief (SASADA; MUNERATO; GREGIANIN, 2013).

4. Discussion

Oral mucositis has a complex etiopathogenesis, configuring a great challenge for oncology, no matter how advanced the

studies are, there are still no definitive therapies, the substances used are empirical and palliative (VOLPATO, 2007).

Oral mucositis cannot be completely prevented, but preventive treatment decreases the severity and duration of cases. Low-level laser therapy has been widely applied, as it is a non-invasive procedure with anesthetic and anti-inflammatory potential. In the case of pediatric patients, despite being indicated, it is still not as popular due to limited evidence (HE et al., 2018).

On the other hand, 0.12% chlorhexidine, despite being an antiseptic that has a great immediate antibacterial and virucidal power, its main indication is the reduction of dental plaque and moderate to severe gingivitis. It is well indicated because in addition to its side effects (extrinsic staining of teeth and tongue) being easy to reverse, it is a broad-spectrum biocide and can reduce most gram-negative and gram-positive bacteria in a short period, varying from 30 seconds to a minute, thereby reducing the risk of further infections. In addition, chlorhexidine alone is not completely effective in reducing the severity of mucositis in all patients, but it is very effective in patients receiving chemotherapy alone (CARDONA et al., 2017).

For Rodriguez et al. (2010), oral mucositis is a very common and highly severe complication, present in patients undergoing oncological treatments in the pediatric sector, requiring increased attention, as it decreases the quality of life and can increase the costs of treatments, due to its potential for reach the gastrointestinal tissues causing severe ulcerative lesions, for example. Ulcerative mucositis that usually appears after seven days of treatment and is more present in patients who are being treated for solid tumors or in cases of transplantation, increasing the chances of infections due to immunocompromise and poor inflammatory response, causing greater risks, which can lead to the patient to secondary complications and even death.

5. Conclusion

Oral mucositis is one of the main acute side effects induced by cancer treatment, ranging from localized erythema to extensive ulcers in the oral cavity, which can be aggravated by inadequate oral health, as in the case of pediatric patients, who are often affected with more severe forms.

It is noteworthy, after the present study, the need for the patient diagnosed with cancer to be assisted by a multidisciplinary team, even before starting cancer therapy. There is a need for follow-up with the dentist for oral adequacy and health education for the family, addressing children's oral hygiene, to reduce the chances and severity of oral mucositis. The importance of this prevention is due to the direct impact on the quality of life of the affected patient, especially with the most severe forms of OM, which can lead the patient to malnutrition and interruption of cancer treatment, with a risk of early death.

Despite studies, the treatment of OM is still controversial. Efforts by a multidisciplinary team must be made to improve the general well-being of the patient, therefore, more

research is needed to arrive at a precise and specific protocol, so that there is a therapeutic evolution and reduction of morbidity and mortality.

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