Original Article

Motor Alterations Favor the Occurrence of Oral Mucositis in Pediatric Oncology Patients

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Abstract

Objective: To identify the predictive factors for the appearance of oral mucositis (OM) in pediatric oncology patients based on their motor alterations. **Material and Methods:** This study was an observational, cross-sectional study with 2-19-year-old patients undergoing treatment at the pediatric oncology outpatient service of the Napoleão Laureano Hospital in João Pessoa, Brazil. The convenience sample consisted of 42 patients aged 2 to 19 years with a first diagnosis of cancer and under treatment. The instruments used were a questionnaire with sociodemographic questions - the modified Oral Assessment Guide (OAG) - and some categories of the International Classification of Functioning Disability and Health (CIF), applied by a calibrated examiner (Kappa>0.65). The data were organized in Excel spreadsheet and analyzed descriptively and inferentially using logistic regression (α=5%). **Results:** Most patients were female (52.4%, n=22), mean age of 11.6 years, median 12.0 years, self-declared as non-white (61.9%, n=26), non-white (66.7%, n=28), family monthly income of up to 2 Brazilian minimum wages (88.1%, n = 37). Most patients presented hematologic neoplasia (54.8%, n=23) with acute lymphoid leukemia (36.6%; n=15) and most of them were subjected to chemotherapy (45.2%; n = 19). OAG identified oral mucositis in a few cases (23.8%, n=10). Logistic regression and odds ratio showed that individuals with moderate and mild difficulty in changing basic body position had, respectively, 19.7 and 30.8 times more chances of developing oral mucositis. In patients with severe motor impairment, this risk is 17.3 times greater and those with mild difficulty in taking care of the bodily parts had an increase of 33.4 times the risk for oral mucositis. **Conclusion:** The deficit in motor activities increased the chances of developing oral mucositis.

Keywords: Child; Neoplasms; Stomatitis; Motor Activity; Logistic Models.

Introduction

In the last 40 years, the treatment for childhood cancer has shown continuous improvement and these advances have been attributed to a more effective use of anti-leukemic agents, the intensification of treatment when required, the identification of prognostic factors for risk stratification, and the improvements in supportive care [1]. The treatment options are surgery, chemotherapy, radiotherapy, bone marrow transplantation and immunotherapy, alone or in combination, depending on the indication for each case [2,3]. In the same way as cancer cells, normal cells with a high mitotic activity, such as cells from the oral mucosa, gastrointestinal mucosa, bone marrow and skin, are also susceptible to the action of cancer treatments [4].

The oral cavity suffers a great impact of the anticancer treatment, the main side effects being mucositis, xerostomia, candidiasis, hemorrhage, radiation caries, dysgeusia, neurotoxicity, osteoradionecrosis, trismus and dentinal hypersensitity, apart from fungal, herpetic and bacterial infections. It is known that mucositis, xerostomia, hemorrhage and infections occur three times more often in children than in adults [2,5-7]. Other complications related to the anticancer treatment and its oral alterations are discomfort and pain, which may result in nutritional deficit, impaired immune response and a longer hospitalization time, increasing the risk of death [8].

Other deleterious effects of the antineoplastic treatment are the motor alterations and impairments, such as reduction of active and passive joint amplitude, along with loss and/or decrease of muscle strength, decrease of motor skills, limitation of functional mobility and loss of physical conditioning, which may lead to reduction in cardiorespiratory capacity, weight gain and growth hormone alterations. These changes altogether affect the functional status and the quality of life of oncology patients [9,10].

Advance of research in this perspective is necessary to understand the patient's health condition during the anticancer treatment, as well as the most prevalent alterations that arise with the start of therapy. New studies in this field may guide multidisciplinary practices to prevent or minimize secondary complications, contributing to a more efficient health care and a better quality of life for the patients.

Given the above, the objective of this study was to identify the predictive factors for the onset of oral mucositis in pediatric oncology patients with motor impairments.

Material and Methods

Study Design and Sample

This was an observational, cross-sectional and analytical study with follow-up of a population with cancer undergoing treatment at the pediatric oncology outpatient service of the Napoleão Laureano Hospital in the city of João Pessoa, capital of the state of Paraiba, located in the northeastern region of Brazil, considered the easternmost part of the Americas and the country. The study was developed from April to September 2017.

Population

The study population consisted of pediatric oncology patients treated at the pediatric oncology outpatient service of the Napoleão Laureano Hospital (HNL) and their parents/caregivers. Convenience sampling and convenient accessibility were used for selecting a sample of 42 children and adolescents aged 2 to 19 years diagnosed with some form of neoplasias and admitted at the Napoleão Laureano Hospital pediatric oncology outpatient service.

All patients aged between 2 and 19 years undergoing anticancer treatment (chemotherapy, radiotherapy and/or surgery) and with a primary diagnosis of malignant neoplasia were considered eligible for this study. Patients with chronic diseases and compromised health status were excluded from the study.

Data Collection

Before data collection, a pilot study was carried out to test the instruments, materials and method proposed for the study. Five individuals selected by convenience who fulfilled the inclusion criteria were subjected to an interview. Although overall positive, the results showed that some adaptations should be done in the data collection instrument, such as the use of synonyms and a simpler language, without changing the meaning of the categories related to the International Classification of Functioning, Disability and Health (ICF), to improve the understanding of younger participants and avoid misinterpretation.

The instrument used for this study presented three sections: the first contains questions regarding socioeconomic and clinical issues; the second contains questions from the modified Oral Assessment Guide (OAG) [11]; and the third section contains questions from ICF's activity and participation domains. Data collection was performed by a previously trained and calibrated examiner (Kappa>0.65).

The following variables were considered for the study: presence of mucositis, sex, age, skin color, education, family monthly income, type of neoplasias (hematological or solid tumors), type of treatment, changing basic body position (d410), maintaining a body position (d415), transferring oneself (d420), lifting and carrying objects (d430), moving objects with lower extremities (d435), fine hand use (d440), hand and arm use (d445), walking (d450), moving around (d455), moving around in different locations (d460), moving around using equipment (d465), using transportation (car, bus, train, plane, etc). (d470), driving (riding bicycle and motorbike, driving car, etc.) (d475), riding animals for transportation (d480), hygiene (bathing, drying, washing hands, etc.) (d510), caring for body parts (brushing teeth, shaving, etc.) (d520), personal hygiene related to the processes of excretion (d530), dressing (d540), eating (d550), drinking (d560), Looking after one's health (d570). The questionnaire was applied to the participants at HNL's wards and dental office, which had suitable conditions to perform this phase of data collection. This phase of the study lasted 20 to 30 min on average, including the examiner reading the questions and examining the patient's oral cavity, as required by the OAG. In cases where there was a cognitive and/or speech impairment, the

questions were made to the parent/caregiver or proxy informant. Data collection required use of the following materials: hospital bed and/or reclining chair, clinical ladder, white coat, gloves, disposable mask and cap and hand lights or reflectors.

Statistical Analysis

The data were first inserted in Excel spreadsheets and then transferred to the R software (The R Project for Statistical Computing, version 3.3.1). Data were analyzed using descriptive and inferential statistical methods. Descriptive analysis used frequencies, means and standard deviations.

For inferential statistics logistic regression was used to identify the variables associated with the onset of mucositis in the patients and thus aid in the decision-making process to minimize its occurrence. Each independent variable was analyzed for the test of predictive factors by univariate regression analysis, adopting a 0.30 statistical significance level for selection of the variables to be used for the adjustment of the multiple model. Adjustment of the final model was performed using the backward method with a significance level of 0.05. Then it was evaluated the model adjustment, sensitivity, specificity and predictive values, as well as the model explanatory power by analyzing the area under the receiver operating characteristic (ROC) curve.

Ethical Aspects

The research protocol was approved by the Research Ethics Committee (CEP) of the Federal University of Paraíba (Protocol No. CAAE 63759516.0.0000.5188) and the study was conducted in compliance with the Brazilian National Health Council (CNS) Resolution 466/12, which establishes the ethical standards for conducting research involving human beings.

Results

Forty-two children and adolescents were evaluated, 52.4% (n=22) of them being female and the mean age was 11.6 years (Table 1).

Table 1. Frequency distribution of the characteristics of 2-19-year-old children and adolescents treated at the Napoleão Laureano Hospital.

	Variables	n	%
Sex	Female	22	52.4%
	Male	20	47.6%
Age	<13 years	22	52.4%
	>13 years	20	47.6%
Skin Color	White	16	38.1%
	Non-white	26	61.9%
Education	No education	4	9.5%
	Kindergarten	5	11.9%
	Elementary school	28	66.7%
	Secondary school	5	11.9%

Family Income Monthly	Up to 2 minimum wage*	37	88.1%
	2 to 6 minimum wage*.	5	11.9%
Cancer Type	Hematological type	23	54.8%
	Solid tumor	19	45.2%
Treatment	Chemotherapy	19	45.2%
	Surgery	3	7.2%
	Chemotherapy + Radiotherapy	4	9.5%
	Chemotherapy + Surgery	11	26.2%
	Chemotherapy + Radiotherapy + Surgery	5	11.9%
Mucositis	Present	10	23.8%
	Absent	32	76.2%

*Brazilian minimum wage: $300.99; Dollar course April 2017: R$3.1130

Regarding the self-reported skin color, 61.9% (n=26) were non-whites and 38.1% (n=16) were whites. Regarding education, 66.7% (n=28) were attending elementary school and 9.5% (n=4) were out of school. The family monthly income of most participants (88.1%; n=37) was up to 2 Brazilian minimum wages.

Most children and adolescents (54.8%; n=23) had hematologic neoplasias, among which 36.6% (n=15) had a diagnosis of acute lymphoid leukemia. Regarding the solid tumors (45.2%; n=19), the highest prevalence was osteosarcoma (12.2%; n=5). Regarding the antineoplastic treatment, chemotherapy was the most frequently mentioned (45.2%; n=19) followed by the combination between surgery and chemotherapy 26.2% (n=11).

From the data collected with the OAG, it was found that 23.8% (n=10) of the patients presented mucositis. The study used the logistic regression model (LRM) to identify independent variables associated with the presence of mucositis that could compose the final model.

First, each independent variable was submitted to the chi-square test and the variables that presented statistical significance (p<0.3) were included in the final model (Table 2). It is important to note that due to the variety of subcategories of some variables, such as the skin color, education, walking, among others, they had to be grouped for the chi-square test in order to identify whether they were indeed significant for the model. Without this clustering, variables relevant to the model could be excluded.

Table 2. Explicative variables and their p values relative to the endpoint (p<0.3).

Variables	Significance
Education	0.263*
Changing basic body position (performance)	0.111*
Walking (performance)	0.035*
Moving around (performance)	0.219*
Maintaining a body position (capacity)	0.005*
Transferring oneself (capacity)	0.035*
Lifting and carrying objects (capacity)	0.035*
Walking (capacity)	0.207*
Moving around in different locations (capacity)	0.064*
Caring for body parts (brushing teeth, shaving, etc.) (capacity)	0.018*

*p<0.3.

The Backward method was then used for selection of variables in the logistic regression. This procedure removes the variable with highest p value, one at a time, and is repeated until only significant variables are left to obtain a model that can explain the event of interest. A 5% significance level was set for variable selection ($\alpha=0.05$) (Table 3).

Table 3. Significant variables in the adjusted logistic regression model.

Variables	Parameter Estimation	Standard Error	p value	OR	IC95%[OR]
Intercept	-3.421	1.039	0.000		
Changing basic body position (performance – mild difficulty)	3.427	1.745	0.049	30.78415	27.3639 – 34.2043
Maintaining a body position (capacity – moderate difficulty)	2.979	1.375	0.030	19.66814	16.9731 – 22.3631
Moving around (capacity – severe difficulty)	2.853	1.485	0.054	17.33972	14.4291 – 20.2503
Caring for body parts (brushing teeth, shaving, etc.) (capacity – mild difficulty)	3.510	1.369	0,010	33.44827	30.7656 – 36.123

*Significant p-value <0.05

The final model selected 4 of the 51 initial variables that presented statistical significance (p<0.05): changing basic body position (performance); maintaining a body position (capacity); transferring oneself (capacity) and caring for body parts (brushing teeth, shaving, etc.) (capacity). It is worth noting that the variable "transferring oneself " remained in the model because it presented a p value close to the significance level and because it is an important variable to justify the final model.

After defining the model, its validity must be verified. Therefore, the function deviation or deviance measures the discrepancy between the saturated model (best model) and the study model [12]. The deviance statistics of the adjusted logistic regression model (24.8913) is lower than the reference chi-square value (52.19232), considering the adequate model.

Adjustment quality of the obtained model can also be checked using the ROC curve, which is a graph of sensitivity versus false positive rate. The accuracy of the diagnostic test is proportional to the area under the curve, i.e., the larger the area, the more accurate the test. Thus, a decision rule based on the "cutoff point" is adopted, which summarizes the probability in a dichotomic response [12]. Individuals with an estimated probability lower and higher than the cut-off point are classified as patients with absence and presence of mucositis, respectively. According to the ROC curve, it was observed a cutoff of 0.032, sensitivity of 100.0%, specificity of 81.2% and area under the curve equal to 0.914 or 91.4% (Figure 1).

Among the variables presented in this model, there are those that represent risk factors to the occurrence of mucositis: changing basic body position, maintaining a body position, transferring oneself (capacity) and caring for body parts. Then, the odds ratio of the final logistic regression model variables was calculated to assess the effect of each variable on the likelihood of occurrence of mucositis (Table 4).
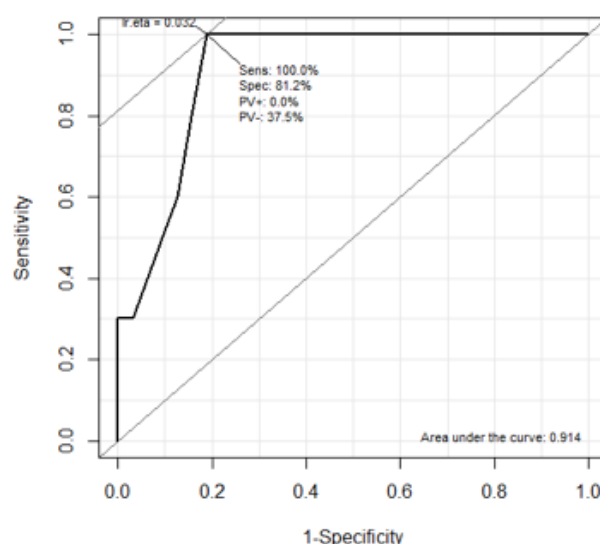
Figure 1. Graph of the ROC curve, specificity and sensitivity.

Table 4. Odds ratio (OR) estimations (p<0.05).

Variables	OR	IC 95% [OR]
Changing basic body position (performance – mild difficulty)	30.78415	27.3639 - 34.2043
Maintaining a body position (capacity – moderate difficulty)	19.66814	1.9731 - 22.3631
Moving around (capacity – severe difficulty)	17.33972	14.4291 - 20.2503
Caring for body parts (brushing teeth, shaving, etc.) (tooth brushing, shaving, etc.) (capacity – mild difficulty)	33.44827	30.7656 - 36.123

According to the found OR values, individuals who have mild difficulty in changing basic body position, even with help, are 30.8 times more likely to develop mucositis while individuals with a moderate difficulty in maintaining a body position have 19.7 times greater likelihood. Individuals with severe difficulty in transferring themselves are 17.3 times more likely to develop mucositis, and those who have mild difficulty in caring for their body parts are 33.4 times more likely to have this oral condition.

Discussion

The anticancer treatment for children and adolescents has an adverse impact on their quality of life, as the therapy may cause complications that affect their routine activities, self-concepts and interpersonal and social relationships [10,13-15]. Based on this, the aim of this study was to identify predictive factors for the onset of oral mucositis in pediatric oncology patients with motor impairments. The number of participants (n=42) agrees with other studies that had similar populations [16-18]. This small sample size can be explained by the low incidence of childhood cancer compared with cancer in adults, accounting to only 1-3% of all malignant tumors worldwide [1]. In the same way as observed in other national and international studies [10,18,19], children at early ages were the most frequently affected.

The results of the present study showed a predominance of cases in females, as observed by other authors [18,20,21], differently from most similar studies that indicate a higher incidence of

cancer in males [2,22-24]. This finding could be explained by a combination of factors: the distribution of the Brazilian female population (51%), the new cancer cases in females estimated for the 2016-2017 biennium [1], and the fact that the state of Paraíba particularly has a higher incidence of cancer in females (51.6%) according to IBGE 2010 data.

The non-white skin color was the most frequently referred, which agrees with another Brazilian study [25] and may be a result of the significant miscegenation of our population.

In agreement with the literature, there was a predominance of hematological malignancies in the present study, and ALL was the most common type [2,26]. It is noteworthy that ALL has its peak incidence between 2 and 5 years, with a remission rate of approximately 80% [27]. Leukemias are the most common malignancies in childhood, accounting for 25-35% of all tumors in patients below 14 years of age [1].

Chemotherapy is the most widely used anticancer therapy. Accordingly, it was the most frequent treatment reported in the present study, alone or in combination with surgery or other therapies, as reported in other studies [17,26]. Chemotherapy is used in approximately 70% of cancer patients, as it has the highest remission rate for many tumors and increases the most the survival rate of patients [26].

The various types of antineoplastic treatment may cause adverse effects to the oral cavity. Oral mucositis is one of the main oral complications [2,6,13] affecting 20-40% of individuals undergoing chemotherapy, 60-85% of those undergoing hematopoietic stem cells transplantation (HSCT) and nearly 100% of those undergoing head and neck radiotherapy [28].

In the present study, the pediatric oncology patients had oral mucositis prevalence of 23.8%, similar to other studies [17,24] but lower than most national and international studies [18,23]. This fact could be attributed to the sample size, diversity of treatment modalities and individual patient response. Oral mucositis is a common and clinically relevant side effect of chemotherapy and radiotherapy, and may affect any part of the gastrointestinal tract. The onset of oral mucositis usually occurs between the 3rd and 4th day after the start of treatment, worsening between the 7th and 14th days, with clinical manifestation varying from mucosa irritation to ulceration [28].

The results of this study showed that motor impairment favors the occurrence of oral mucositis, identifying a statistically significant association between the development of this comorbidity and mild difficulty in changing basic body position, even with help. There was also an association between mild difficulty in caring for bod parts and oral mucositis. It was observed that children and adolescent with cancer realize the limitations imposed by the disease, but parents and professionals' care and warning contribute to restrain even more the autonomy of their activities [29]. However, the development of oral mucositis may be sometimes associated with preexisting caries and periodontal diseases that aggravate due to poor hygiene, creating favorable conditions to the onset of oral mucositis [23,24,26]. A feasible hypothesis is that, during the course of treatment, these remain have long stays in a hospital bed due to cancer side effects, mobility restriction and to medical devices [10], which makes oral hygiene difficult and increases the likelihood of developing

oral mucositis. Adequate oral hygiene can both prevent and accelerate the healing of oral mucositis [28,30].

The outcomes of this study also showed that individuals with severe difficulty in transporting oneself were more susceptible to developing oral mucositis. Studies indicate that children and adolescents with cancer have greater inactivity, reduced muscle strength, musculoskeletal morbidities, fatigue and neurocognitive impairment, and most likely have a sedentary lifestyle, being at higher risk of obesity, growth hormone deficiency and decrease of bone density [10,16]. It is also important to understand that the development of oral mucositis is related not only to the type of anticancer treatment, but also to the patient's oral health status and immune markers, such as inflammatory mediators and immunosuppressors [30]. So, it can be assumed that the motor alterations caused by cancer weaken the patients, decreasing their immunity and increasing the risk of infection/sepsis and the chances of development of oral mucositis.

The results of this study show that this group of patients requires special care and innovative strategies that can improve not only their physical capacity, but also their systemic condition, which reflect on their oral health and quality of life.

This study has limitations. The first one is its cross-sectional design, which analyzes the variables of interest in a single moment in time, biasing the establishment of cause-effect relationships since the changes in the patients' health status during the course of treatment cannot be considered. Another limitation is the sample size, which was small for the number of studied variables, a fact that could influence the association among them. However, even with these limitations, this study contributes to support the decision-making process of health professionals regarding the treatment of pediatric oncology patients by widening the perspectives for more efficient and specific interventions that consider the motor impairments of these children. Further research is required to stimulate new insights on this subject in order to address issues not contemplated in the present study, thus increasing knowledge and proposing interventions to minimize the harmful effects of antineoplastic treatments.

Conclusion

Motor alterations related to dislodgment and self-care increased the chance of children and adolescents with cancer to develop oral mucositis, revealing not only that oral care is important to prevent this condition, but also that attention to the motor deficit may influence positively the oral health.

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