

Salivary Flow in Pediatric Cancer Patients Compared to Healthy Children and Adolescents

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Abstract

Objective: To verify differences between salivary flow in pediatric cancer patients before starting antineoplastic treatment and in healthy pediatric patients. **Material and Methods:** This is an observational, cross-sectional, paired study with sample of 120 children and adolescents (3-18 years). Thirty pediatric cancer patients were selected for convenience at "Napoleão Laureano" Hospital (G1). Another group was composed of 90 individuals attended at the School of Dentistry Clinics of the Federal University of Paraíba, matched by age (G2). Data collection was performed in two steps for both groups. Information regarding pediatric cancer patients was obtained by interview with parents / guardians and searching medical records, while in the other group by interview with parents / guardians. Saliva collection was performed using standard method in both groups: unstimulated salivary flow rate (USFR) being the mean volume expelled in 1 minute. Data were analyzed by the Shapiro-Wilk, Kolmogorov-Smirnov and Mann-Whitney tests ($\alpha = 5\%$). **Results:** Mean USFR for G1 and G2 was 0.52 mL / min and 0.66 mL / min, respectively ($p > 0.05$) and, in both groups, significant difference was observed ($p < 0.05$) between the mean USFR values of its subgroups, and values of adolescents being higher than those of children. **Conclusion:** There is no difference in unstimulated salivary flow of pediatric cancer patients before starting antineoplastic treatment compared with healthy pediatric patients.

Keywords: Neoplasms; Saliva; Dental Care for Children.

Introduction

Decreased salivary flow in pediatric cancer patients increases their risk of being affected by infectious odontogenic processes and gingival and mucosal inflammation, as saliva is a fundamental fluid for maintaining oral cavity homeostasis. The complex composition of saliva is related to its surface cleaning functions, maintenance of stable pH, conservation of dental mineralization, facilitation of cell healing, neutralization of harmful dietary components, protection and influence on microbiota and hydration of mucosal surfaces [1,2].

In pediatric cancer patients, the most common factor associated with hyposalivation or dry mouth sensation is the antineoplastic treatment. Therapeutic protocols are responsible for quantitative and qualitative changes in salivary production [3].

Typical factors for pediatric cancer patients, excluding antineoplastic therapy, are also related to decreased salivary flow, such as stress, psychological depression and anxiety attacks, as well as opportunistic infections, such as candidiasis, which alter salivary excretion [4,5]. In this context, it is emphasized that cancer negatively impacts the quality of life of children and adolescents [6] and that changes in salivary characteristics may contribute to the occurrence of oral comorbidities during antineoplastic treatment [1,7].

Although studies associate changes in the salivary flow of cancer patients under antineoplastic therapy, few studies have evaluated saliva production before cancer treatment is implemented. In this context, it is suggested that situations experienced by children and adolescents diagnosed with cancer, and not yet submitted to antineoplastic therapy, may decrease their salivary flow compared to healthy pediatric patients. The aim of this study was to test this hypothesis.

Material and Methods

General Study Data

This is an observational cross-sectional paired study, adopting an inductive approach and comparative-statistical procedure.

The study was carried out at “Napoleão Laureano” Hospital, a state reference in cancer treatment, where patients from G1 group were selected; and the Federal University of Paraíba, in whose dentistry clinics patients from G2 group were chosen. Data collection took place from March 2016 to October 2017. The selection of pediatric cancer patients was made by convenience, using a non-probabilistic sampling technique, totaling 30 patients (G1 = 30). For each of these, three healthy patients (G2 = 90), matched for gender and age, were selected.

Data Collection

Data collection was performed in two steps for both groups, namely: information regarding patient identification and health status, and saliva collection. Trained researchers were responsible for performing saliva collection. The salivary collection protocol was unstimulated, once per patient, by observing biosafety principles.

Patients from G1 and G2 were instructed to sit with adequate posture, holding a sterile glass container (Dappen Pot) near the mouth, to fix the gaze at one point, with head angled down at 45°, allowing saliva accumulation on the oral floor to then be expelled by the spit. For each patient, this protocol was performed for 2 minutes, during which they could not communicate and perform sudden movements with upper and lower limbs, nor with the tongue.

Group 1 - Cancer Patients

Data related to children and adolescents were obtained by questioning patients and / or their guardians, collecting information such as name, age, skin color; and through medical records, clinical and hospitalization variables, such as blood type, pathology and antineoplastic treatment. These data were obtained under specific conditions for pediatric cancer patients, respecting their health condition and emotional state, because they are in the first phase of contact with the hospital environment, newly diagnosed with cancer, not yet under antineoplastic treatment.

Saliva collection was performed in the morning, between 08:00 am and 11:00 am both for inpatients (in the pediatric ward) and for those without outpatient care. In the ward, salivary collection was performed in beds during individual visits to patients. To standardize procedures, adaptations were necessary so that children and adolescents could sit upright and appropriate to the collection protocol. For this, support of pillows was used, elevation of the headboard and / or sought the help of those responsible.

Group 2 - Healthy Patients

To perform the paired analysis [8], the selection of G2 patients was based on the identification of gender and age of pediatric cancer patients in order to reduce the possibility of confounding factors, being performed at the Dentistry Clinics of the Federal University of Paraíba.

Initially, the study proposal was explained to patients and / or their legal guardians and, once the participation in the research was consented, questions were asked about patient's data such as identification, age, last feeding time and if there was drug administration in the two weeks prior to the research date.

Salivary collections were performed respecting the same positioning standards and methodology established for G1.

Salivary Flow Measurement and Classification

After collection, saliva was transferred to eppendorfs and salivary flow was determined by means of the milliliter markings arranged on the long axis of the deposit. Unstimulated salivary flow was measured in mL of saliva produced every minute (mL / min), dividing the expelled salivary volume by the number of minutes of active fluid excretion [9].

Salivary flow was classified according to parameters proposed by the University of Malmö for unstimulated salivary flow per minute [10], being categorized as normal, low or very low. Flow

was considered normal for values above 0.25 mL / min; low for values between 0.1mL / min and 0.25 mL / min; and very low for values below 0.1 mL / min.

Data Analysis

Initially, the t-test was applied to independent samples in order to verify the homogeneity of groups in relation to patients' age, and no difference between groups was observed ($p = 0.11$). Regarding gender, the Chi-Square test was applied, and it was observed that groups were homogeneous ($p = 0.39$). Descriptive data analysis was performed to verify the frequency of variables and central tendency and dispersion measures.

Salivary flow data of patients from both groups were submitted to the Shapiro-Wilk and Kolmogorov-Smirnov normality tests ($\alpha = 0.05$). Since the distribution of salivary flow averages in G1 and G2 was not normal, the verification of the difference between them was performed using the Mann-Whitney test ($\alpha = 0.05$).

In addition, taking into account that within the age group of 0-19 years, there are differences between older and younger patients, groups were divided into two subgroups: children (3 to 9 years) and adolescents (10 to 18 years), and in each of them, the average USFR was verified. In these subgroups, salivary flow averages were compared by the Mann-Whitney test ($\alpha = 0.05$). Data were analyzed using the SPSS 21.0 software.

Ethical Aspects

The research was approved by the Research Ethics Committee of the Health Sciences Center, Federal University of Paraíba, under CAAE 45800415.7.0000.5188.

Results

Tables 1 and 2 show the socio-demographic characteristics of pediatric cancer patients and healthy children and adolescents, respectively.

Table 1. Characterization of pediatric cancer patients at a referral hospital.

Variables	N	%
Gender		
Male	11	33.7
Female	19	63.3
Age Subgroups		
Children	15	50.0
Adolescents	15	50.0
City		
João Pessoa	09	30.0
Other Cities	21	70.0
Base Neoplasms		
Hematological	24	80.0
Non Hematological	06	20.0

Table 2. Characterization of healthy pediatric patients.

Variables	N	%
Gender		
Male	41	45.6
Female	49	54.4
Age Subgroups		
Children	65	72.2
Adolescents	25	27.8
City		
João Pessoa	87	96.7
Other Cities	03	3.3

The average salivary flow presented by pediatric cancer patients before starting antineoplastic treatment was 0.52 mL / min (\pm 0.41 mL / min). The median was 0.39 mL / min, with maximum and minimum values, respectively, of 0 mL / min and 1.60 mL / min.

Taking into account that the age of patients may influence their salivary production, G1 was divided into two subgroups: children (under 10 years) - n = 15; and adolescents (from 10 to 19 years old) - n = 15. The mean unstimulated salivary flow for children was 0.36 mL / min. (\pm 0.31mL), median of 0.35 mL / min, minimum value of 0.0 mL / min. and maximum value of 1.30 mL / min. The average value verified for adolescents was 0.68 mL / min. (\pm 0.44 mL), median of 0.60 mL / min, minimum value of 0.07 mL / min. and maximum value of 1.60 mL / min. (Figure 1).

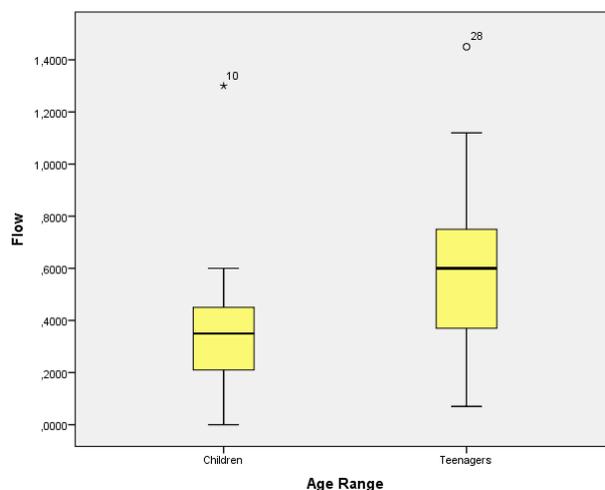


Figure 1. Comparison between salivary flow averages (mL / min) of children and adolescents with cancer from a referral hospital.

The subgroup of children under 10 years of age showed non-normal mean distribution of USFR values according to the Shapiro-Wilk normality test, while the subgroup of adolescents showed normal distribution according to the same test. Thus, both subgroups were compared by the Mann-Whitney U Test and statistically significant difference ($p=0.023$) was found.

The average salivary flow of G2 patients was 0.66mL / min. (\pm 0.59 mL / min), with median of 0.50 mL / min. The highest value found for unstimulated salivary flow of healthy children and adolescents was 2.70 mL / min, while the lowest value found was 0.02mL / min. (Figure 2). The

average salivary flow values of this group were organized in a non-normal distribution, according to the Kolmogorov-Smirnov test ($p < 0.05$).

For this group, dichotomization was also performed to broaden the understanding of unstimulated salivary flow by age group. Likewise, subgroups were children and adolescents with average USFR of 0.96 mL / min for adolescents and median of 0.50 mL / min, while for children, the average value was 0.46 mL / min and median of 0.83 mL / min, as shown in Figure 2. Both subgroups presented non-normal distribution of mean salivary flow values, according to the Kolmogorov-Smirnov test. Thus, the Mann-Whitney U test was applied for comparing them, through which statistically significant difference was found between them ($p = 0.002$).

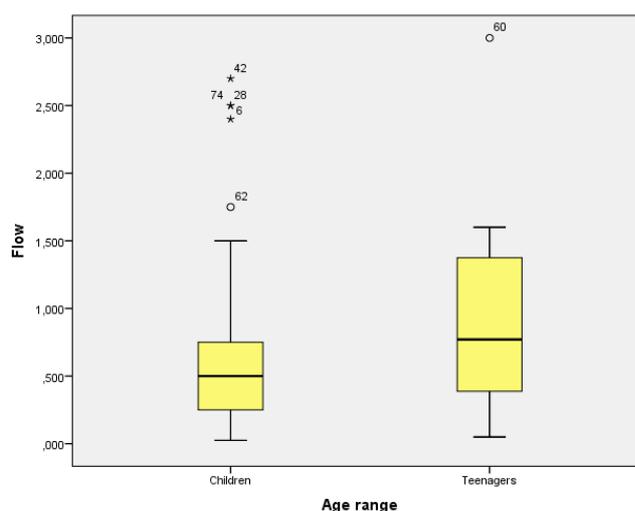


Figure 2. Comparison between salivary flows (mL / min.) of children and adolescents treated at Federal University of Paraíba.

Both groups presented non-normal distribution and thus Mann Whitney U test was applied to compare USFR between G1 and G2. It was found that there is no difference in unstimulated salivary flow between healthy and oncological pediatric patients before antineoplastic treatment was implemented for pediatric cancer patients ($p = 0.725$).

Discussion

Similar to results found in this study, the literature points out that hematological tumors are the types of tumors that most affect children and adolescents worldwide, and are the main causes of morbidity, differing from neoplasms in adults, in which hematological tumors are a minority, representing only 6.2% [11]. CICI-3 (International Classification of Child Cancer) confirms that hematological neoplasms are worldwide and historically the main causes of childhood cancer [12].

The base pathology that most affected children and adolescents was acute lymphoblastic leukemia (ALL), with prevalence of 53.3% ($n = 16$). Studies show similar results in Europe [13] and the United States [14], justifying such prevalence due to the inadequate immune system development of these individuals, which would lead to severe infectious reactions, culminating in the

onset of ALL [14]. There is a consensus in international literature that this type of leukemia is the most common childhood cancer, and the one that most kills individuals under 20 years of age [15], age group of patients in this study.

The salivary flow rate of pediatric cancer patients in this study (0.52 mL / min) is higher than that found in a referral center in Campinas, Brazil, for children and adolescents (6-16 years) with Hodgkin's Lymphoma before starting the radiotherapy protocol, whose mean USFR was 0.3 mL / min [16]. In Poland, it was found that the USFR of children with acute leukemia before chemotherapy treatment was less than 0.5 mL / min - value corresponding to the average flow of healthy patients [17], being also lower than the average found for pediatric cancer patients in this study.

However, when comparing with other studies that measure salivary flow in healthy patients of different age groups, the values obtained are lower. In one of them [18], the average salivary flow of schoolchildren aged 0-6 years was 1.23 ± 0.59 mL / min. In contrast, another study [19] recorded average unstimulated salivary flow for healthy pediatric patients of 1.69 mL / min for those aged 6-11 years, and 1.25 mL / min for those aged 12-14 years. As the flow of healthy patients is greater, regardless of age, it is suspected that other variables may cause salivary flow impairment in pediatric cancer patients, such as psychological and physiological factors specific to cancer.

In a multicenter study [20], the aim was to compare the salivary flow of children in seven different places, including countries. Among these countries, the one presenting values similar to those of the present study was Brazil (state of Rio de Janeiro), with average unstimulated salivary flow equivalent to 0.61 mL / min. (± 0.34 mL), which could be justified by the climate similarity, which would influence the patients' circadian rhythm.

The normal flow produced by all salivary glands of a healthy individual in one minute would be from 0.3 to 0.5 mL [21]. In another study, the mean of USFR values for healthy children and adolescents were 0.35 mL / min [20]. It is noteworthy that all the above values, considered normal, are below the average for pediatric cancer patients at the baseline of this study, which may be justified by methodological differences.

Given the classification proposed by the University of Malmö [10], it was observed that pediatric cancer patients in the present study, before antineoplastic therapy, had normal condition regarding USFR (73.3%, n = 22); however, a percentage of 26.6% of these patients had lower than expected flow, considered low (13.3%, n = 4) or very low (13.3%, n = 4).

Salivary flow values for G1 subgroups (younger and older than 10 years) differ from results found in another study [19] for healthy patients in two respects: the average salivary flow values for both subgroups found by these researchers were higher, and they found higher salivary flow in children (1.69 mL / min.) than in adolescents (1.25 mL / min.).

A plausible explanation for such disagreement is the difference in the categorization of age groups, in this study, individuals aged 6-11 years are considered children and those aged 12-14

years, adolescents. In addition, healthy patients selected in the study¹⁹ would be subject to fewer flow-reducing factors than pediatric cancer patients, even before starting antineoplastic therapy.

The mean USFR value in G1 differs from results found in literature [22], in which healthy individuals aged 7-18 years presented average salivary flow of 0.36 mL / min (\pm 0.2 mL / min); almost half of the value found by this research. In another study [20], results were closer to those observed in this research, with average salivary production of 0.61 mL / min (\pm 0.34 mL / min). The results found in another study conducted in Rio de Janeiro exceed salivary flow values pediatric patients in the state of Paraíba, reaching average of 1.23 ± 0.59 mL / min [18]. The variations found by salivary flow surveys are generally due to the methodological variability of saliva collection, whose production is still sensitive to variations in positioning, time, and climate.

According to the salivary flow categorization performed by the University of Malmö [10], the majority of G2 patients, 75.6% (n = 68), presented normal salivary flow values, while 16.7% (n = 15) of them showed low flow, and 7.8% (n = 7) very low flow.

As in G1, for healthy patients, mean USFR values, both in the subgroup of children and adolescents, diverged and were lower than those observed in another study [17]. The comparison between the mean flow of healthy children in this study and that shown by the above researchers (1.69 mL / min) shows greater discrepancy than the comparison between subgroups of adolescents in both studies.

The scarce literature addressing this theme reveals similar results [14]. When comparing salivary flow averages of pediatric cancer patients in baseline and healthy patients, it was also found that there were no differences between groups. Similar results were obtained in another study [17], which evaluated the salivary flow of Polish pediatric cancer patients and that of healthy pediatric patients. Thus, these studies indicate that it is not the cancer itself - except salivary gland neoplasms - that produces changes in the salivation of cancer patients; but cytotoxicity and metabolic changes caused by cancer therapies [23,24].

Although there was no difference in unstimulated salivary flow between pediatric cancer and healthy patients, in absolute values, the average salivary flow for pediatric cancer patients was lower than the average observed in healthy patients.

This difference, however slight, is understandable due to the context of an individual newly diagnosed with cancer, especially a child or adolescent, such as the frequent administration of palliative medication while antineoplastic treatment cannot be instituted and stress, anxiety and psychological distress caused by the disease [23,24]. All the factors above are recognized in literature because they negatively influence salivary flow, but there are no studies proving this relationship in pediatric cancer patients before they start antineoplastic therapy providing a real decrease in salivary flow [25-27].

In addition, it is relevant to consider that the percentage of individuals from G1 that had very low salivary flow [10] was 13.3%, which is almost twice the same category for G2, which presented percentage of 7.8% of individuals with very low salivary flow.

This finding has clinical relevance considering that this condition represents a risk factor for greater microbial colonization, dental caries and infections, among other oral diseases, since saliva has the function of cleaning the oral cavity by removing food residues and bacteria, in addition to ensuring homeostasis of the oral cavity [28].

It is important to note that the lack of statistical difference in unstimulated salivary flows between groups may have occurred due to the limitations of this research, such as the small sample, especially in G1. However, it is known that the disease under study is considered rare in literature and since this study was performed at the reference center for cancer treatment in the state, it is understood that there is sample representativeness with the population of children and adolescents with cancer in the state of Paraíba.

Therefore, further studies are needed to better understand the factors and mechanisms that influence the salivary production of pediatric cancer patients before starting the therapeutic protocol, in order to point out new targets for treatment of hyposalivation comorbidity and improve the quality of life of these patients. The results of the present study may provide subsidies for such studies and help understanding the oral health care demands of these patients.

Conclusion

The unstimulated salivary flow of pediatric cancer patients before starting antineoplastic therapies does not differ from that observed for healthy children and adolescents. A significant percentage of children and adolescents with cancer, not yet treated for this disease, have low to very low salivary flow. The subgroup of children deserves special attention in dental management regarding preventive measures because these children have lower mean unstimulated salivary flow value compared to adolescents.

Authors' Contributions: PMMB and RCC designed the study, performed the data collection, data analysis and interpretation, wrote the manuscript and reviewed the manuscript. ILAR and AMGV designed the study, performed data analysis and interpretation, wrote the manuscript and reviewed the manuscript. PRFB and SAS performed data interpretation and reviewed the manuscript. All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest: The authors declare no conflicts of interest.

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