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COMPARISON OF THE LEVELS OF IL-6, S-IGA, PH, AND SALIVARY FLOW RATE ON DENTAL CARIES IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Abstract:

Objective: *The study was aimed to evaluate the amount of dental caries in children with Acute Lymphoblastic Leukemia (ALL) were in the maintenance phase of chemotherapy.*

Material and Methods: *This is a case-control and analytic study conducted on the 27 children (4-12 year old) with ALL who were in the maintenance phase of chemotherapy in the Ahvaz Shafa Hospital, Iran. The participants of the control group, matched in terms of age, gender, and cultural status with the case group, were selected among the healthy children referred to Ahvaz Razi Hospital, Iran. From all participants, the saliva samples were collected to assess the immunologic factors, including IL-6, IgA, PH, and saliva flow rate. The number of decayed (D), missing (M) and filled (F) teeth were recorded based on the WHO (DMFT) index and without the use of radiography. Then, after radiographic assessment, the exposed sample saliva was collected from the subjects to assess the immunologic factors, including IL-6, IgA, PH and salivary flow rate.*

Results: *The amount of salivary IgA in children with ALL is less than the control group and was statistically significant ($P < 0.05$). However, no significant difference was observed in the rate of IL-6 and DMFT between the two groups ($P > 0.05$). Saliva flow rate and salivary PH in children with ALL were significantly lower than the healthy counterparts ($P < 0.05$).*

Conclusion: *Children with hematological diseases require special dentistry attention along with antineoplastic therapies. Hygiene and oral care in these patients compared with children who do not have blood problems must be performed more carefully.*

Keywords: *acute lymphoblastic leukemia, DMFT, IL-6, IgA, salivary pH, salivary flow rate*

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INTRODUCTION:

Leukemia is a white blood cell cancer affecting bone marrow. As the disease progresses, cancer cells enter into blood circulation. This disease is usually diffused proliferation of lymphoid and myeloid cells colony and it can exist in chronic and acute forms (1). Acute leukemia is more common than chronic leukemia which includes 55% of all leukemia cases (1). Appearance of chronic type is rare in children being the reason for less than 2% of all types. Approximately, one out of every 29000 children suffers from leukemia in the United States every year. Acute leukemia is the reason for one third of all childhood cancers. About 80% of such children suffer from lymphocytes (acute Leukemia Lymphocytes (ALL) (2). Proliferation is controlled mono colonial immature lymphoid cells in bone marrow and peripheral blood found in children including 25% of all children Neoplasm and 80% of Leukemia in children. It is more prevalent in boys rather that girls (1).

Dental caries is a contagious infectious disease and many factors are at work for onset and development of the disease. Dental caries is a preventable disease. It begins normally from tooth enamel and develops slowly in its first stages. It has been shown that this disease (tooth in mouth) needs food culture and uric acid bacteria. Saliva, food, and bacteria make biofilms (plaque) which sticks to the surface of the tooth. As time passes, substrates serve as nutrient used by bacteria. Therefore; bacteria produce acids which can destroy tooth minerals. Flow rate, concentration, ability to neutralize acid- base and capacity of remineralization of saliva minerals to teeth are among well-known characteristics of saliva influencing development, remission and adjustment of the disease in some cases (2).

Considering the physical health problems of children with leukemia, having dental treatment are done under certain conditions and some limitations (2). On the other hand, since these children should be hospitalized for a long time, there will be many problems regarding preventive dental plans and diet control. Previous studies in this regard have shown contradictory findings. Furthermore, there is no published study on the oral health status and risk factors of children with leukemia who were hospitalized in Ahvaz Shafa Hospital, Iran. Therefore, the present study was aimed to comparatively investigate the safety factors influencing the decay, salivary flow, saliva buffering capacity, and DMFT in the children with leukemia who are undergoing chemotherapy in maintenance phase and their healthy counterparts.

MATERIALS AND METHODS:

This is a case-control and analytic study conducted on the 27 children (4-12 year old) with ALL who were in the maintenance phase of chemotherapy in the Ahvaz Shafa Hospital, Iran. The participants of the control group, matched in terms of age, gender, economic and cultural status with the case group, were selected among the healthy children (n=27) referred to Ahvaz Razi Hospital, Iran (3). The main inclusion criteria included the patients in a chemotherapy maintenance phase or 3 months after that period. Moreover, they received the same medications consisting of Mercaptopurine (9 MP) daily, methotrexate (MTX) weekly, vincristine (VCR) monthly and prednisolone tablets in the first 5 days of every month. The patients with the history of receiving radio therapy, bone marrow transplant, and any other systemic diseases were excluded from the study. The sampling sites for both case and control groups were public hospitals affiliated with the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

At first, we explained the procedure for both the patients and their legal parents. Moreover, we reminded them that there will be no problem in case they reject participating in the study.Then, written informed consent was obtained from the patient and his/her legal parents. Since eating nutrients like fruit, juice, vitamin supplements, tea and coffee can influence saliva, we requested patients not to have such nutrients 1 hour before sampling. Saliva samples were gathered during morning between 8 to 11 a.m. for all the samples. An anonymous questionnaire was designed to visit patients in which there was individual information like: age, sex, education level of parents and determining WHO based DMFT index. We used DMFT index (decay, missed, filled) to evaluate dental health care condition (milk teeth in children under 7 year old and permanent ones in children above 7 year old). The index shows number of teeth decayed, missed and filled.

The teeth with structural imperfections such as Amelogenesis Imperfecta and Dentinogenesis Imperfecta were excluded from the study. Decay diagnosis was performed without radiography assessment through two techniques: 1) Observing visual changes in the teeth color and 2) consistency of tooth surface together with the help of sense of touch and feeling softness when using catheter.

In next step, the data of salivary features such as the flow rate and amount of saliva and PH were recorded for all children. Finally, the oral health tips and a pamphlet consisting instructions about useful health tips were provided for all the patients and their parents with. Those cases that needed treatment had been referred to treatment centers.

Sample collection in stimulated Saliva

Due to low volume of saliva in the leukemia children, we used stimulated saliva to measure the level of secretion between the case and control subjects. The patient chewed tasteless paraffin (1 g with melting point 42 ° C) for 45 times or 1 minute and let his saliva pour into sterile tube from his lower lip (4). Stimulated Salivary Flow (SSF) velocity should be 2-1 ml/min regarding amount of saliva gathered (2). The values lower than 0.5 ml/min are considered as abnormal velocity.

Measurement of Saliva Safety Factors

Two methods were used for assessing salivary safety factors: The IL-6 measurement method and IgA measurement method which were performed as follows:

IL-6 measurement method:

The assessment kit manufactured in Uroimmune Co., Germany and designed based on ELIZA method using ELIZA sandwich technique was used to measure IL-6.

IgA measurement method:

The assessment kit built in Autoimmune Co., Germany was designed based on ELIZA method using sandwich ELIZA technique to measure IL-6. Salivary IgA ELIZA test is basically operating upon IgA connection to two anti IgA agents.

Finally, the data gathered were analyzed with statistical package SPSS version19 using independent T test for quantitative parameters and Chi-square test for qualitative parameters. The $P< 0.05$ was set as statistical significance for all tests in the study.

RESULTS:

The participants of this study were divided into 2 groups of case (patients) and control (healthy children) (each n= 27). The patient group consisted of 8 girls and 19 boys (age range = 7-29 year old) and healthy group of14 girls and 13 boys (age range = 7 to 22 year old) (Table 1).

The comparisons of average values between patient and healthy groups are presented in Table 2.

Table 1. The gender frequency distribution of patient and healthy groups studied separated

Sex / Group	Boy	Girl	Total
patient	19 (70.5%)	8 (29.5%)	27 (100%)
healthy	13 (48.5%)	14 (51.5%)	27 (100%)

Table 2. Comparisons of average values between patient and healthy groups.

Group / Variable		Patient	Healthy
Saliva flow rate (ml/min)		0.79	1.4
IL-6		188.02	171.79
IgA		18.07	38.18
DMF	<7	4	5.7
	7≤	2.4	1.2

Table 3. Result of indexes comparison between healthy and patient groups

Variable	IL-6	IgA	Saliva flow rate	PH
significant	0.06	0.001	0.00	0.00

Table 4: DMF comparison between two groups of patient and healthy studied

	Test Statistics	Freedom Degree	P value
<7	14.2	11	0.2
7≤	4.96	7	0.6

There was a significant statistical relationship between patient and healthy groups in IgA (P< 0.05) (Table 3). However, there is not a significant statistical relationship between 2 groups regarding IL-6 (P> 0.05). Results show that saliva flow rate in children with ALL was less than healthy peers and the difference was statistically significant (P< 0.05). Moreover, PH comparison showed that saliva PH in children with leukemia was significantly lower than the healthy individuals (P< 0.05).

Chi-Square parameter test was used to compare DMF values between patient and healthy groups (Table 4).

There was no statistically significant relationship between the two groups regarding the values of DMF index (P> 0.05).

Then, relationship between DMF and other variables in patient and healthy groups were studied using correlation coefficient. Correlation coefficient between variables ranges from -1(maximum reverse relationship between two variables) to +1(maximum direct relationship between two variables. The statistical significance level was set as P≤ 0.05 for these statistical analyses.

Table 5: The correlation coefficients of the relationship between DMF and other variables in the patient group.

Result of test / Variable	Correlation Coefficient	P value
Age	- 0.07	0.72
Sex	- 0.21	0.28
Saliva flow rate	- 0.21	0.28
PH	0.04	0.83
IL-6	0.26	0.17
IgA	- 0.18	0.36

Considering results of the Table 5, DMF has a significant relationship with IL-6 which is not statistically significant.

Table 6: Relationship between DMF and other variables in the healthy group

Result of test / Variable	Correlation Coefficient	P value
Age	- 0.39	0.04
Sex	- 0.19	0.33
Saliva flow rate	- 0.43	0.02
PH	- 0.02	0.91
IL-6	0.55	0.003
IgA	- 0.25	0.2

Results showed that DMF has only a direct relationship with IL-6 which is statistically significant.

DISCUSSION:

In this study, IgA average level and PH in Leukemia children saliva was less than control group and it was a statistically significant difference between these two groups. In this study, IL-6 average level in Leukemia children saliva was more than control group but such difference was not statistically significant. Moreover, DMFT in patient children under 7 year old was more than healthy one and DMFT in patient children above 7 year old was less than healthy ones but there was no statistically significant difference. Stimulated saliva average in Leukemia children was less than control group and there was a significant difference between these two groups.

Wahlin et al. reported that level of saliva secretion in leukemia patients was less than healthy individuals at the beginning of cytotoxic treatment which is decreased after 1 to 3 days and again increases in such a level that it is seen in healthy individuals (4). Main et al. also reported a continuous decrease in saliva secretion in individuals stricken with cancer after 3 months treatment with cytotoxic drugs which is less than healthy individuals in the control group being similar to the findings of our study (5). This is due to the anxiety caused by chemotherapy since previous studies show that psychological stress can decrease saliva secretion (6). On the other hand, patients taking cytotoxic drugs themselves are susceptible to have dry mouth and difficulty in chewing (7).

Findings of our study show a significant difference between s-IgA in leukemia and healthy individuals. This difference can be attributed to the effect of chemotherapy and cytotoxic drugs on immune system being suppressed as well. These findings are consistent with the findings of Main et al. (5). Moreover, Mandel et al. in consistent with our finding reported a reverse relationship between salivary flow rate and IgA accumulation level in healthy individuals, but not in patients during chemotherapy. They attributed the low level of IgA to significant decrease in saliva flow rate (8). They attributed this. This can be due to the preventive effect of chemotherapy drugs on the activity of local cells responsible of IgA secretion (8-10). The other reason for this can be the effects of drugs on salivary glands (5).

In contrary to our findings, Morales- rojas et al. observed no statistically significant difference in safety factors influencing on teeth decay status including IL-6 between children with ALL and healthy peers (11). They found a significant increase in the level of IL-6 TNF alpha 4 days after chemotherapy intervention in the salivary samples of patients with leukemia. Moreover, they showed that IL-6 is secreted from salivary damaged cells (Epithelial, Endothelial, and connective tissue cells) as a local defense (11). Such findings were in line with studies of Sonis (12) and Hont et al. (13). Findings of our study showed a positive correlation between DMF and IL-6 level which is statistically significant in the control group. Increase in DMF level increased the salivary IL-6 level in the individuals of the group control that indicates that increase in salivary IL-6 level raises the risk of decay in healthy children but this positive correlation was not significantly different with the patient group. Gornowicz et al. found similar results as ours. They said that high level of IL-6, TNF alpha in patients with tooth decay causes decrease in the number of osteoblasts, fibroblasts, demineralization of tooth structure and development of the caries. IL-6 together

with other factors can cause bone loss and stimulate production of cytokines (11, 14, 15).

DMF average level in the patient group was less that the control group in our study. This shows that healthcare condition in leukemia children is better than healthy ones. Oral health condition in children with Leukemia during anti-neoplastic treatment period by Pels and Mielnik-Blasz showed that oral health condition in this group was significantly better than healthy ones in control group. This shows that Leukemia patients are being examined more regarding oral health during treatment with anti-neoplastic drugs (16). Findings of our study showed a statistically significant difference between PH in children with leukemia and control group. Findings of the previous studies showed that leukemia leads to reduced PH and alterations in bicarbonate buffer system due to making change in electrolyte levels (17). Considering low PH, oral flora changes from minus gram bacteria to positive gram (18). Findings of our study showed that salivary IgA level in children with ALL was significantly lower than healthy counterparts. Moreover, children with ALL showed significantly lower levels of PH compared to healthy peers.

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