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Effect of Probiotics on Salivary Flow Rate and pH in Children with Acute Lymphocytic Leukemia (ALL) During Chemotherapy

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ABSTRACT

Background: This study was performed to evaluate the effects of probiotics on salivary flow rate and pH in children with Acute Lymphocytic Leukemia (ALL) during chemotherapy.
Methods: A randomized clinical trial was conducted on 11 children with ALL on induction and consolidation phases of chemotherapy. At the beginning, clinical examination of the oral mucosa and dental hygiene and interview regarding the presence of dry mouth were performed. Saliva samples were collected in the morning between 09.00-12.00 a.m., before and after 7 and 14 days gargling with probiotics. Each participant was instructed to gargle probiotics for 60 seconds, morning and night, for 14 days. Descriptive analysis was performed to compare salivary flow rate and salivary pH before and after 7 to 14 days gargling, using Paired t-test because the data is normally distributed (P<0.05).
Results: 7 (63.6%) out of 11 patients complained of a dry mouth sensation. Before gargling probiotics, salivary flow rate and salivary pH were 0.52 and 6.8, respectively. After 14 days of gargling with probiotics, there was a significant increase in salivary flow rate to 0.64 (P<0.05), while salivary pH changed unsignificantly to 6.99 (P>0.05).
Conclusion: Gargling with probiotics in children with ALL during induction and consolidation chemotherapy phase, after 14 days showed a significant increase in salivary flow rate but unsignificant change in salivary pH.

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Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children (80%) and the incidence increases by the age.[1, 2] The incidence of the cancer increases by 1% every year.[3, 4]

Chemotherapy is the cornerstone of treatment in childhood leukemia and almost 90% of children with ALL can be cured with multiagent chemotherapy.[5] Chemotherapy consists of induction, consolidation, and long term maintenance associated with intrathecal CNS prophylaxis given at determined intervals during chemotherapy. Besides damaging cancer cells, chemotherapy can cause oral mucosal toxicity by inhibiting repair processes of the epithelial cells in the oral mucosa, and salivary gland atrophy. The disruption of salivary secretion results in decreased salivary flow rate or xerostomia.[6-10]

Xerostomia is a subjective feeling of oral dryness that can be characterized with or without hyposalivation or reduced salivary flow rate. Other manifestations in the oral cavity are mucositis, opportunistic infections, gingival inflammation, bleeding, dysgeusia and oral soreness.[11-14] Oral manifestations occur 5-10 days following the initiation of antineoplastic therapy and last for 7-14 days.[15] Oral mucositis occur in more than 90% of children under 12 years old who undergo chemotherapy.[11] Reduction in salivary flow rate is associated with decrease in salivary pH due to the reduction in salivary buffer capacity.[11, 16,

[17] Although salivary gland dysfunction associated with chemotherapy appears to be temporary, it may cause discomfort because it is usually accompanied by oral dysgeusia and dysphagia. These conditions increase susceptibility to dental caries, periodontal disease, and oral mucosal infections which in turn greatly interfere with nutrient intake and oral hygiene so that it negatively impacts the success of cancer therapy.[18]

Probiotics, as defined by WHO are living microorganisms which if given in adequate quantities can provide health benefits to the host. Probiotics are normal human microflora that play an important role in health including oral health.[19] Microorganisms often used in probiotics are usually strains belonging to the genus of Lactobacillus. They belong to a group of lactic acid bacteria that produce organic acids (lactic acid) which have an antimicrobial effect. The mechanism of action of probiotics is to prevent cellular adhesion and invasion of pathogenic bacteria, modify the environment, and modulate systemic and local inflammatory immune responses. Probiotics can be useful in preventing oral infections including dental caries, periodontal disease, and even halitosis.[20] Probiotics may influence the composition of saliva that can affect the amount of saliva secreted.[21] Therefore, it can help reduce the risk of oral dryness.[22] Probiotics can also neutralize acidic conditions in the mouth thus affecting salivary pH.[23] As a result, probiotics have been used as an alternative treatment for the prevention of oral toxicity i.e. mucositis.[24]

Materials and Methods

A randomized clinical trial was conducted on 11 pediatric patients with ALL who were admitted to Dharmais Cancer Hospital and Kramat-128 Hospital in Jakarta, Indonesia, between August and November 2019. The children were receiving chemotherapy in the induction or consolidation phase and could follow instruction to gargle and spit out into a tube provided.

The study began by providing information about the procedures and distributing informed consents to be filled in and signed by the parents of each participant. Demographic data of the participants, including gender, age, and data related to the underlying disease were collected from the patient's medical record. Chemotherapy regimens were established according to the hospital protocols.

First of all, interviews to obtain information about the presence of dry mouth sensation or mouth sore was performed. Examination of the oral cavity and oral health status was assessed by calculation of decayed-missing-filled teeth/decayed-extract-filled teeth index, the existence of plaque, calculus index, and dry mouth, the presence of gingivitis and mucositis by evaluating the degree of mucositis using modified Oral Assessment Guide (OAG).[25]

Collecting Saliva Samples

Prior to sampling, participants were asked to rinse their mouth with mineral water for one minute, then discarded or swallowed. The saliva samples were collected from participants before and after 7 and 14 days of probiotic gargling. The saliva was collected from the floor of the mouth of the participants in upright position. This step was repeated 5 times or until 2 ml of saliva was obtained.

The first salivary sampling was done before participants started using probiotics, between 09.00-12.00 a.m. and at least 1-1.5 hours after participants had breakfast. Then, participants had to gargle their mouth with probiotics every day for 14 days. During the procedure, participants first rinsed their mouth with mineral water, then gargling with probiotics for 60 seconds; twice a day (morning and night) was performed which was finally discarded. After gargling, participants were not allowed to eat or drink for 30 minutes. The second saliva sample was taken after the participants gargled their probiotics for 7 days and the third sample after gargling for 14 days. Each sample was examined for salivary flow rate calculated in ml/min and salivary pH measured by digital pH meter (ETI pH meter Ltd.). The equipment was calibrated with distilled water to reach pH 7 each time of use.

Results

A total of 11 participants from 16 pediatric ALL patients were enrolled in this study, 4 (36.4%) were male and 7(63,6%) female, between 4-18 years (mean age 9.55±4.61 years old). 9 (81.8%) had high risk features. The period of chemotherapy ranged between 2-19 weeks, 5 (45.5%) were in the induction and 6 (54.5%) were in the consolidation phase. The commonly chemotherapy regimens used included dexamethasone, vincristine, daunorubicin, intravenous methotrexate 1000 mg and intrathecal methotrexate.

All participants who had received prior chemotherapy were found to have mild to moderate mucositis (OAG score 9-16), and complaints of dry mouth sensation existed in 7 (63.6%) participants.

The salivary flow rate was >0.1 ml/min at the baseline sample. Table 1 shows the increase of salivary flow rate after 7 days gargling with probiotics which was unsignificant ($P \geq 0.05$). However, a significant increase in the salivary flow rate was found after 14 days gargling with probiotics ($P<0.05$). Taking into account the heterogeneity of the participants, it was found that the data distribution was not normal (Table 2).

There was an increase in salivary pH after 7 days gargling with probiotics. Meanwhile, salivary pH continued to increase after 14 days of gargling. However, changes in salivary pH before and after gargling with probiotics were not statistically significant (Tables 3 and 4).

Table 1: Results of comparative analysis of salivary flow rate (mL/min) before and after 7 days gargling with probiotics

Variable	N	Mean (SD)	P value*
Before gargling	11	0.57 (0.18)	0.055
After 7 days gargling	11	0.71 (0.28)	

*Paired t-test, significant $P<0.05$

Table 2: Results of comparative analysis of salivary flow rate (mL/min) before and after 14 days gargling with probiotics

Variable	N	Median (min-max)	P value *
Before gargling	11	0.52 (0.39-1)	0.036
After 14 days gargling	11	0.64 (0.4-2)	

*Wilcoxon Signed Ranks Test, significant P<0.05

Table 3: Results of comparative analysis of salivary pH before and after 7 days gargling with probiotics

Variable	N	Mean (SD)	P value*
Before gargling	11	6.8 (0.23)	0.471
After 7 days gargling	11	6.91 (0.58)	

*Paired t-test, significant P<0.05

Table 4: Results of comparative analysis of salivary pH before and after 14 days gargling with probiotics

Variable	N	Mean (SD)	P value*
Before gargling	11	6.8 (0.23)	0.198
After 14 days gargling	11	6.99 (0.51)	

*Paired t-test, significant P<0.05

Discussion

Oral manifestations frequently consist of xerostomia, mucositis, opportunistic infections, gingival inflammation, bleeding, dysgeusia and oral soreness.[11-14] These oral manifestations usually occur 5-10 days following the initiation of antineoplastic therapy and last for 7-14 days.[15] Side effects in the oral cavity occur in more than 90% of children under 12 years who undergo chemotherapy.[11] Xerostomia refers to the sensation of oral dryness with or without hyposalivation.[26] Based on criteria proposed by WHO, xerostomia was present when there were subjective complaints of oral dryness; although, in terms of objective measurement, there was no evidence of hyposalivation.[11]

It has been mentioned that chemotherapeutic agents from the group of antimetabolites and cytostatic antibiotics can cause direct damage to the salivary glands including acinar degeneration, swelling of acinar and ductal cells, glandular vasoconstriction, imbalance of fluid and electrolyte, and alteration of fluid movement from plasma through salivary acinar cells to the ductal system and finally into the oral cavity which result in disruption of salivary secretion.[8, 9, 17] In a study by García-Chías *et al.*, dry mouth was a major complaint in 73.4% of patients undergoing chemotherapy.[3, 13] Dry mouth can cause difficulty in eating, speaking and predisposes to oral candidiasis, traumatic lesions, dysphagia, and increased caries risk.[27] Beside the xerostomia, mucositis is an alteration in salivary condition that affects microbiome composition in the oral cavity.

Glucocorticoids (e.g. Dexamethasone) are commonly used as an immunosuppressive agent. Their use concomitantly with other chemotherapy agents can induce several oral toxicities.[18]

Saliva plays an important role in maintaining stable oral health. Alteration in salivary conditions including salivary flow rate and pH will cause changes in the oral environment. Reduced salivary flow rate causes dry mouth, although dry mouth is not always marked by reduced salivary flow rate. Reduced salivary flow rate makes salivary composition decreased and the function of saliva in protecting the oral cavity is not optimal, thus dental caries and other oral toxicities can occur. Moreover, acidic salivary pH can provide an enabling environment for pathogens to grow and will aggravate the condition.

Alteration in salivary flow rate can be caused by intake of food and water, body position, stress or emotional state, systemic disease, nausea, exposure to light, size of the salivary glands, body weight, age, gender, level of exercise, circadian rhythms, as well as consumption of drugs including chemotherapy agents.[28] Salivary secretion is also influenced by both mechanical and chemical stimuli, where acid is a strong stimulus for increasing salivary flow rate.[29] Meanwhile, the concentration of the electrolytes in the saliva is associated with changes in salivary pH and its flow rate.

The positive effects of probiotics on oral health has been reported elsewhere.[19, 20, 30] Literature data on the administration of probiotics as gargling in patients with malignancy and mucositis are still limited. A prospective study in 60 children with ALL who underwent chemotherapy and were given probiotics for 30 days, showed that probiotics can help reduce gastrointestinal symptoms due to chemotherapy.[31] Another study analyzing the effect of probiotics on the oral cavity in a population aged 18-75 years and children aged 6-14 years showed positive impact. The study indicated that probiotics were potentially effective in reducing morbidity, improving clinical symptoms and reducing oral candidiasis. It is well known that Candida albicans is a pathogen that causes oral mucositis. The mechanism of action of probiotics includes competition with pathogenic microorganisms for nutrient and receptor acquisition and their antimicrobial properties against oral Candida overgrowth.[32]

In our study, there was an increase in salivary flow rate after 7 and 14 days gargling with probiotics. These results were in accordance with other studies about chewing gum with probiotics in 54 adults with hyposalivation; showing the impact of daily chewing of probiotic

gums for 12 weeks on salivary flow rate, salivary IgA levels and salivary pH. It was stated that chewing, as a mechanical stimulus could increase the salivary flow rate, with or without probiotics.[33] Hatakka *et al*. suggested the administration of probiotic cheese could increase salivary flow in elderly subjects.[34] From this study, it can be interpreted that probiotics may help to reduce the risk of hyposalivation and dry mouth sensation.[22] This is also supported by another study that administration of probiotics for 60 days can increase saliva secretion. There was an increase in the mean unstimulated and stimulated saliva from baseline after 60 days. The mean pH at baseline was also increased after 60 days. The increase in salivary flow rate in this study might influence the composition of saliva, thereby affecting the nature and amount of saliva secreted.[21]

Increased salivary flow rate might also be caused by acidic stimuli contained in probiotics. Microorganisms in probiotics are a group of lactic acid bacteria that produce organic acids (lactic acid).[35] Almost similar to the study using chewing gum containing probiotics as a mechanical stimulus, in this study the gargling action was used as a stimulus for salivary secretion.[33] Probiotics can also modify intraoral environment by modifying oral cavity pH, thereby inhibiting the development of pathogens.

Acidic compounds theoretically decrease salivary pH, but in the present study salivary pH increased after 7 and 14 days gargling with probiotics. This was following an increase in the salivary flow rate. The increase in salivary flow results in increase in the pH of the saliva to a very small extent.[36] As the salivary flow rate is increased, it would increase the volume of saliva and its electrolyte content, including bicarbonate. The function of bicarbonate is to neutralize the decrease of salivary pH. In another study, the production of ammonia from urea or arginine by lactobacillus bacteria contained in probiotics has been shown to improve efficiently salivary buffer function.[35] The increase in salivary flow rate and pH in this study was statistically insignificant except for the increase in salivary flow rate after 14 days. This difference was probably due to the varying admission period according to patient conditions, especially children with ALL during chemotherapy. Intake of food before sampling, diversity of the protocols and chemotherapy regimens were other possible reasons for this difference.

Conclusion

Based on this study, gargling with probiotics in 14 days was associated with significantly increased effect on salivary flow rate and increased pH in children with ALL during chemotherapy.

Authors' Contributions

T. Damayanti designed the study, performed data collection, data analysis, interpretation, and drafted the manuscript. M. Suharsini and S.B. Budiardjo designed the study, performed data collection, data analysis, interpretation, drafted and reviewed the manuscript. All authors declared that they contributed to the critical review of intellectual content and approval of the final version to be published.

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