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Effect of Oral Cryotherapy In Preventing Chemotherapy Induced Oral Stomatitis Among Childhood Acute Lymphoblastic Leukemia

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Abstract: *Oral stomatitis is the most common problem of children with Acute Lymphoblastic Leukemia (ALL) taking chemotherapy as side effect. It can cause erythema, crackle, inflammation, ulceration, and bleeding on the oral mucosa including lips. Oral cryotherapy is an alternative preventive method towards the etiology of oral stomatitis which has local vasoconstriction effects. This study aimed to investigate the effect of oral cryotherapy in preventing chemotherapy induced oral stomatitis among childhood ALL. This quasi experimental study was conducted in Hematology - Oncology Unit (HOU) of Yangon Children Hospital (YCH) in Myanmar. In this study, fifty numbers of children with ALL were selected through consecutive sampling method. Half of all participants (control group n=25) received only routine oral care and the other half (study group n=25) was provided routine oral care plus oral cryotherapy for 5 minutes prior chemotherapy and up to 15 minutes after chemotherapy. Oral mucosa conditions of all participants before and on the 3rd day of chemotherapy were assessed with Eiler's oral assessment guide (1988). Data were analyzed using SPSS version 16. Results revealed that all participants (n=25 in each group) in both groups had healthy oral condition before chemotherapy. However, on the 3rd day of chemotherapy, 44% of the all participants in the control group developed oral stomatitis and study group remained unchanged at healthy oral cavity and. Oral mucosa conditions before and on the 3rd day of chemotherapy were significant different between study group and control group with p value < 0.05. It was concluded that oral cryotherapy had the preventable effect on the chemotherapy induced oral stomatitis if plain ice cube is prepared with strict consideration according to this study and if it is applied to every chemotherapeutic drug. Further research studies should be done to assess oral cavity on 5th, 7th, and 14th days of post chemotherapy.*

Keywords: *Oral Cryotherapy, Stomatitis, Chemotherapy, Acute Lymphoblastic Leukemia, Children.*

I. Introduction

Every year, over hundred subtypes of childhood cancers were detected around 300,000 children under the age of 20 years all over the world. Among them, the most prevalent types of cancer in this age group were leukemia, brain cancer, and lymphoma (Pediatric Cancer Research Foundation, 2019). Leukemia is a cancer of blood-forming cells from the bone marrow and is seen in children and teens mostly. American Cancer Society (ACS, 2019) stated that almost 1 out of 3 childhood cancer in children under the age of 15 is leukemia and about 3 out of 4 leukemia among the children is acute lymphoblastic leukemia.

Until the last decades of the 20th century, cancer cells had not been controlled satisfactorily from its active proliferation. By that time, patient suffering from cancer was denoted as victim whose disease condition also deliberated gradually. Treatments did not response or control on the cancer cell proliferation at that

time. Cancer patient did not have any chance over the praying to the gods to have the increased survival rate (Myers and Beare, 2001; Sudhakar, 2009).

Nowadays, cancer have various options of advanced treatments with the thanks of science such as either single or combination of surgery, chemotherapy, radiation, bone marrow or stem cells transplantation. Among them, chemotherapy is the primary treatment of favored in childhood cancers included ALL. Chemotherapy has the anti-proliferation effects against cancer cells that have quick growth and increased the survival rate. American Cancer Society estimated the five years survival rate of childhood ALL with 91% in the developed countries (ACS, 2019).

On the other hands, anti-proliferation effects of chemotherapy impact on the healthy tissues that proliferate quickly such as bone marrow and gastric mucosa as side effect. One of the most common side effects of chemotherapeutic drugs is the stomatitis; a painful inflammation and ulceration of oral mucous membrane included cheek, lips, tongue, palate and floor of the mouth by disrupting the important barriers of oral mucosa and normal saliva activity. Occurrence of stomatitis is higher in aggressive cancer therapy among children population with hematological malignancies in compared with children suffering from other malignancies (Anil et al., 2018).

As detail; oral stomatitis had the risk of 90% in head and neck cancer patients subjected to chemo-radiotherapy, 99% in patients undergoing high dose myeloablative chemotherapy for hematopoietic stem cell transplant, and 80% in the children with leukemia undergoing chemotherapy. Moreover, incidence and severity of oral stomatitis is higher three times in childhood cancer than adulthood and also higher in children with hematological malignancies than other malignancies (Anil et al., 2018).

According to the statistic of HOU (YCH) in Myanmar (2018), total admission of childhood cancer was 350 and childhood ALL was 80 in 2017. Incidence rate of oral-stomatitis was about 73% (n=65) of all children with ALL undergoing chemotherapy. Among them, oral stomatitis Grade I was 13.5% (n=12), Grade II was 33.6% (n=30), Grade III was 16.8% (n=15), and Grade IV was 9% (n=8) by WHO oral mucositis assessment scale (1981). Moreover, almost all children with ALL have ever had oral stomatitis problems frequently, especially, at the time of induction remission, escalated methotrexate, and consolidation phase. The children have been experiencing the problems of dry mouth, ulceration of oral mucosa and lips, feeding difficulties and have difficult to talk. Sometimes, bleeding from the ulcerated anus can be seen when defecated.

For a person, mouth is the main food receiving entry and the person with such problems triggers the consequent problems of underweight, fluid and electrolyte imbalance, anemia, and infection. The worse the patients' consequence problems are, the more prolonged the hospitalization time will be. Some patients having the combination problems of bone marrow depression may reduce the capability of tolerating to the planned treatment. Such problems may cause discontinuation of treatments and up to 40% increase of mortality of patients (Eilers and Million, 2012).

Hanan et al., (2014) and Anil et al., (2018) also highlighted that dose reductions rates have 60% of patients and discontinuation of regimens is about 30% in such problems. In Myanmar, there has little difficulty to present the dose reduction and discontinuation rate of planed regimens. However, expert persons at HOU (YCH) provided the information regarding dose reduction problems and prolonged hospitalization due to oral stomatitis are also occurred frequently.

Such patients have the double burden of physical and psychological stresses as well as the family experience the care burden on the children having oral stomatitis with ALL underwent chemotherapy (Eilers and Milion, 2012). Many researchers have examined various strategies including pharmacological and non-pharmacological measures to control and prevent the chemotherapy induced oral stomatitis. Among them, oral cryotherapy is the well-validated, simple, cheap and effective strategy in clinical setting; however, there is still weakness to apply (Hanan et al., 2014; Rose, 2015; Mishra et al., 2017). Also in Myanmar, preventive measures are still needed towards the etiology of oral stomatitis.

II. Significance to Nursing

It can provide the helps to implement new changes in the life long care of individuals and is used to develop treatments and preventive measures that provide the most optimum level of care.

III. Objective of the Study

This study was to investigate effect of oral cryotherapy in the preventing of chemotherapy induced oral stomatitis among childhood acute lymphoblastic leukemia.

IV. Research Hypothesis

Children who receive oral cryotherapy with routine oral care will have healthier oral cavity compared to children who receive only routine oral care.

V. Research Methodology

5.1. Research Design

A quasi experimental research design was used in this study.

5.2. Setting

This study was conducted at Hematology- Oncology Unit (HOU) of Yangon Children Hospital (YCH).

5.3. Study Period

The study was conducted from October 2018 to October 2019.

5.4. Study Population

The study was conducted on the children aged ≥ 5 years with ALL who underwent chemotherapy in HOU of YCH.

5.5. Sample size calculation

To fulfill the objective, sample size was calculated by using the formula of Lwanga & Lemeshow (1991). In which data was used from the study conducted by Hanan et al., (2014) who studied the effect of oral cryotherapy on the occurrence of stomatitis by induced chemotherapy among the children with bone tumors in Egypt.

5.6. Sampling

The participants of the present study were selected by consecutive sampling technique. To circumvent from the exposure risk of control group and study group, control group of 25 participants were studied at first for two weeks. After the control group had completed, another 25 participants of the study group were studied the last two weeks.

5.7. Research Tool

Part-A: participants' age, sex, and educational level were collected as background characteristics, and clinical characteristics were collected with history of chemotherapy, laboratory results of the child, and types of oral cryotherapy application for this study.

Part-B: Eiler's oral assessment guide (1988) which was developed by Eiler, Berger and Peterson in 1988. It can assess eight items: ability of swallow, lips and corner of mouth, tongue, saliva, mucus membrane, voice, gingivae, and teeth. And, it has a three point scale that is used for answer /responses as the following: score one indicates to normal findings, score two for mild abnormality without compromise of either mucosal integrity or loss of function, and score three for severe abnormality with compromise of either mucosal integrity or loss of function.

The total scores equal 24 marks covered 8 items and was categorized as the following: 1 to 8: indicates healthy oral cavity, 9 to 16: indicates moderate stomatitis, 17 to 24: indicates sever stomatitis. Permission for this instrument was received from the authorized person of Pediatric Nursing Department at Akdeniz University Faculty of Nursing in Turkey. Reliability of this instrument has 0.96 of Cronbach's alpha (Hanan et al., 2014).

5.8. Pilot Study

Pilot study was conducted on 10 percent of total sample size for one week. The instrument did not need to revise or was found feasible to continue for the main study. However, sampling procedure was modified to circumvent from the exposure risk of control group and study group. The control group was studied at first and the study group was after completion of control group.

5.9. Data Collection Method and Procedure

Approval of Ethic and Research Committee of University of Nursing (Yangon) and formal permission from each authorized persons were obtained at first. Plain ice cubes were prepared under the strict considerations. Approval of free from bacteria and chemical on ice cube was obtained through the laboratory tests at National Health Laboratory (NHL). Demographic data was collected from the participants with proforma of this study. Before chemotherapy session, the oral health conditions of participants in each group were assessed prior by using Eiler's oral assessment guide (1988).

For control group: participants were studied only the oral health condition before and after 3rd days of chemotherapy who received the only routine oral care of HOU (YCH).

For study group: participants were administered routine oral care of HOU (YCH) with oral cryotherapy. Oral cryotherapy was provided to study group 5 minutes prior to chemotherapy. Participants were asked to maintain and moved the ice cubes in their mouth continuously during administration of chemotherapy and up to 15 minutes after the chemotherapeutic agents. Children who did not tolerate sucking the ice cubes for whole planned duration were allowed to suck for an intermittent duration. Post-test data of oral health condition in both groups were evaluated after 3rd days of chemotherapy by Eiler's oral assessment guide (1988).

5.10. Data Analysis

Data entry, data clean up, data summarization and data analysis were carried out by computer using statistical package for social science (SPSS) software version 16. The Shapiro-Wilk normality test was used to determine the distribution of the collected data. Demographical and clinical characteristics were described by frequency and percentage. Chi square and Fisher's exact test were used to determine the differences of pre-existing demographical and clinical characteristics of participants between the study group and the control group. Mann-Whitney U test was used to compare the significant difference of continuous variable between two groups and Wilcoxon Signed Rank (paired) test was used for within both groups. Significant level was considered with p-value <0.05.

VI. Results

In this study, the control group (n=25) received the only routine oral care and the study group (n=25) was provided the routine oral care plus oral cryotherapy. Among the study group, twenty numbers (80%) of participants could have tolerated the oral cryotherapy with the continuous dose and the other 5 numbers (20%) participants took the oral cryotherapy with intermittent dose.

Table (1) showed that the demographic characteristics of participants in both groups before receiving chemotherapy. This table revealed that the most participants in the both groups were the age of <9 years (64%, n=16 in the study group and 72%, n=18 in the control group). As gender, male population distribution was higher than the female population in both groups with just over two times in the study group and three times in the control group. In education, the highest distribution rate of education level in the study group was Primary level with n=13 (52%) and those in control group was Pre KG n=13 (52%). Base line characteristics did not have significant difference between the study group and the control group with *P*- value > 0.05.

According to Table (2), all participants were the children with ALL and the majority of participants in both groups had 6 months to 1 year duration of disease. Over the half of all participants in both group had the neutrophil count (≥1.500/mm3) as base line (64%, n=16 in the study group and 76%, n=19 in the control group). All participants took the chemotherapy with various phases. However, most of all participants were found at Intensification phase with 28% (n=7) in study group and 44% (n=11) in the control group. Most distribution of chemotherapy regimen was M.CO.CS and M.V. These regimens took 30 to 60 minutes to accomplish the entire chemotherapy regimen. Before intervention, clinical characteristics of participants between the study group and the control group did not also have significant difference (*p*-value >0.05).

Table (3) showed that existing total scores of oral mucosa of each participants in both groups have the similar scores ranged of 1-8 (Healthy oral health) with the percentage of 100% (n=50) and healthy oral cavity before chemotherapy. Table (4) proved that oral mucosa condition of the study group changed into oral stomatitis and having the significant difference between the study group and the control group on 3rd days of chemotherapy with *p*-value <0.001.

Table (5) showed that having the significant changes of pre and post oral health condition within control group (*p* value < 0.05) and those within study group did not have significant changes (*p* value > 0.05) with Wilcoxon Signed Rank (paired) test. Although pre interventional oral assessment scores of participants between the study group and the control group did not have significant difference (*p*-value >0.05), post interventional oral health condition between the study group and the control group had the significant changes on 3rd days of chemotherapy (*p* value < 0.05) with Mann-Whitney U test. These were described in the Table (6).

Table (1): Comparison of demographic characteristics of participants between the study group and the control group before receiving chemotherapy

Demographic Characteristics	Study group		Control group		χ^2	*p* value
	n	%	n	%		
Age						
<9 years	16	64%	18	72%	0.368	0.544
9 to 12 years	9	36%	7	28%		
Gender						
Male	17	68%	19	76%	0.397	0.529
Female	8	32%	6	24%		
Educational status						
Pre KG	9	36%	13	52%	1.827	0.361*
Primary	13	52%	11	44%		
Middle	3	12%	1	4%		

The result is significant at *p* < 0.05 ***Fisher's exact test**

Table (2) Comparison of clinical characteristics of participants between the study group and the control group before intervention

Clinical characteristic	Study		Control		χ^2	*p* value
	n	%	n	%		
Duration of disease						
<6 months	8	32%	11	44%	2.138	0.428*
6 months to 1 year	13	52%	13	52%		
>1 year	4	16%	1	4%		
Phase of chemotherapy						
Induction phase	1	4%	1	4%	4.692	0.314*
CNS prophylaxis phase	6	24%	6	24%		
Escalated MTX phase	5	20%	6	24%		
Interim maintenance phase	6	24%	1	4%		
Intensification phase	7	28%	11	44%		
Regimen of Chemotherapy						
M.V.DO	0	0%	1	4%	11.877	0.078*
M.V.A.DO	0	0%	4	16%		
M.V.CO.CS	4	16%	1	4%		
M.CS	0	0%	2	8%		
M.CO.CS	9	36%	8	32%		
M.V	8	32%	7	28%		
V.DO	1	4%	1	4%		
M.A.DO	0	0%	1	4%		
V	3	12%	0	0%		
Duration of drug administration						
<30 minutes	7	28%	5	20%	0.439	0.742
30 to 60 minutes	18	72%	20	80%		
Baseline neutrophil						
<1.500	9	36%	6	24%	0.857	0.269
≥1.500	16	64%	19	76%		

The result is significant at $p < 0.05$ ***Fisher's exact test**

Table (3): Oral mucosa condition of all participants in each group before receiving chemotherapy

Oral assessment score before treatment	Study		Control	
	n	%	n	%
Healthy (1 to 8)	25	100%	25	100%
Moderate (9 to 16)	0	0%	0	0%
Severe (17 to 24)	0	0%	0	0%
Total	25	100%	25	100%

Table (4): Oral mucosa condition of all the participants in each group on 3rd day of chemotherapy

Oral assessment score after treatment	Study		Control		Fisher's exact test	*p* value
	n	%	n	%		
Healthy oral cavity (1 to 8)	25	100%	14	56%	14.522	<0.001
Moderate oral stomatitis (9 to 16)	0	0%	9	36%		
Severe oral stomatitis (17 to 24)	0	0%	2	8%		
Total	25	100%	25	100%		

Table (5): Comparison of total oral assessment scores within study group and control group (n=25 in each group)

Group	Pre intervention		Post (3rd day of chemotherapy)		Z	*p* value
	Mean	SD (±)	Mean	SD (±)		
Study	8.0	0.0	8.0	0.0	0.00	1.00
Control	8.0	0.0	10.16	3.67	-2.94	0.003

The result is significant at $p < 0.05$

Table (6): Comparison of total oral assessment scores between the study group and the control group (n=25 in each group)

Oral assessment score	Group	Mean	SD (±)	Mann-Whitney U	Z	*p* value
Pre intervention	Study	8.0	0.0	312.5	0.00	1.000
	Control	8.0	0.0			
Post intervention	Study	8.0	0.0	175	-3.681	<0.001
	Control	10.16	3.67			

The result is significant at $p < 0.05$

VII. Discussion

According to the findings of this study, both groups had preexisting healthy oral health cavity before chemotherapy. When compared oral assessment scores between the study group and the control group, totally 100% of study group had the constant healthy oral cavity on 3rd day chemotherapy. However, control group experienced the various changes of oral health condition in which 44% of the participants developed oral stomatitis. The comparison of two groups indicated that oral cryotherapy with routine oral care was significantly more effective than only routine oral care at p value <0.05. The effect of oral cryohterapy in the prevention of chemotherapy induced oral stomatitis was confirmed with the previous studies among different study population.

A study in Turkey (Baydar et al., 2005) reported that the effect of ice therapy on the adult population (n= 40) with 99 times of cycles with 5-FU chemotherapy for gastrointestinal malignancy. Cryotherapy was administered to the same patient in one course and who was not given in the next course. Cryotherapy was given from the beginning chemotherapy until 10 minutes after chemotherapy. Oral health assessment was done on 5th days, 10th days, 15th days, and 21st days of chemotherapy with WHO toxicity criteria. Oral stomatitis was seen in 6.7% of the courses given with cryotherapy and 38.9% in courses given without cryotherapy.

The results of this previous study supported the present study that the ice therapy had the supportive effect on the incidence of chemotherapy induced oral stomatitis. Difference to the current study was that the participants with ice therapy also developed oral stomatitis. This may be due to uncertain preexisting oral health condition of the participants before chemotherapy. Prior oral stomatitis can influence on the incidence of the oral stomatitis and inflammation can also be exacerbated with preexisting bacterial or fungal infection (Cheng et al., 2011; Sobue et al., 2018). Therefore, oral assessment and oral hygiene care should be provided before chemotherapy because good oral hygiene can provide the effect of oral cryotherapy more effectively on the patient receiving chemotherapy.

Another study was a randomized clinical trial study (Heydari et al., 2012) on adult population with breast and colorectal cancer receiving combination chemotherapy such as 5-fluororacil + leucovorin, cyclophosphamide + adriamucin + 5-fluororacil, or cyclophosphamide + methotrexate + 5-fluororacil in Iran. According to the patient- Judged Mucositis scale, study group received oral cryotherapy from 5 minute before to 5 minute after chemotherapy had the lower incidence rate of oral mucostitis (40%) than the control group (77.5%) received no intervention. Oral mucositis developed in 5-10 or 7-14 days following chemotherapy. This previous study approved that the oral cryotherapy had the preventable effect on chemotherapy induced oral mucositis among the patients with cancer receiving combination chemotherapy which was similar with the current study. Difference to the current study was that 65 % of participants in the study group had poor oral hygiene before chemotherapy and developed oral mucositis as post-test condition. These findings pointed out the combination of oral cryotherapy with routine oral care can prevent chemotherapy induced oral stomatitis more effectively than those who used either only oral care or oral cryotherapy.

Furthermore, a clinical trial study (Askarifar et al., 2013) approved that the oral cryotherapy had the effects of reducing severity of chemotherapy induced oral mucositis than saline mouthwash in adult population undergoing stem cell transplantation therapy. Oral mucositis level was evaluated at 3rd, 7th, 14th, 21st days after chemotherapy with WHO scale. According to this scale, cryotherapy group had statically significant of the lower oral mucositis severity rate than the group who received mouthwash on 7th and 14th days and also has positive effective on the cancer patients undergoing blood stem cell transplantation therapy. In the current study, oral stomatitis started on the 3rd day of chemotherapy. It is seem that the difference may be due to different study population, different types and dose intensity of treatment regimen, and oral assessment scale. It is better to know the duration of oral stomatitis if the evaluation of oral health condition can be done up to the resolution time of oral stomatitis.

An additional reference quasi-experimental study also showed that children receiving the ice sucking five minutes before and up to thirty five minutes after completion of chemotherapy had the significant healthier oral cavity than who did not receive (Hana et al., 2014). According to the Eiler's oral assessment guide (1988), children in the study group had the healthier oral cavity with 93.3% than the control group. Control group experienced severe stomatitis with 23.3% of on the 3rd day of chemotherapy. Opposite to the current study, current study could have constant controlled healthy oral cavity on the 3rd day of chemotherapy with 100% in the study group due to applying oral cryotherapy at every chemotherapeutic drug. Every type of chemotherapeutic drugs had the risk of oral stomatitis shortly after administration (Eilers and Milion, 2012; Texas Oncology, 2019).

And in the current study, mostly changes of oral assessment scores have been observed in altered saliva activity and mucous membrane condition among the participants in control group science on the 3rd day of chemotherapy. Severe changes were observed in the thick, ropy or absent saliva activity with 40% (n=10) and cracked tongue condition with 16% (n=4). However, previous study of Brazil by Riberio et al., (2017) described about changes to saliva activity in OAG score (1988) was occurred during 10 weeks of evaluation and alterations to the mucosa were occurred from 2 weeks of chemotherapy in ALL children. The contrast fact to the present study may be the different types and dose intensity of chemotherapeutic drugs applied. Therefore, performing oral assessment not only before chemotherapy but also every day of chemotherapy is very important on the patient receiving chemotherapy with every chemotherapy regimen to record daily changes of oral health condition.

Regarding the type of oral cryotherapy application, increasing the time of application did not lead to greater protection of chemotherapy induced oral stomatitis on the patients following standard dose chemotherapy according to the previous study of Keefe et al., (2007). However, a quasi-experimental study among the children with bone tumors in Egypt showed that about more than half of children who sucked ice continuously had healthy oral cavity than who sucked ice intermittently on the 3rd day of chemotherapy (Hanan et al., 2014).

In the current study, the analyzed findings on the 3rd day of chemotherapy were the same with healthy oral cavity among the participants with either continuous application of oral cryotherapy or intermittent application of oral cryotherapy in the study group. It seems that these differences come from the different types and dose intensity of chemotherapy regimens among these studies. It is also necessary to investigate further studies regarding the optimum duration and intensity of cryotherapy.

Overall, cryotherapy plus routine oral care had prevented chemotherapy induced oral stomatitis than only routine oral care among the children with ALL. This may be due to the application of the additional oral cryotherapy on the routine oral care at every chemotherapeutic drug because all chemotherapeutic drugs may alter the oral cavity activity and oral stomatitis was the direct effect problem of chemotherapy (Eilers, 2004). These findings have been confirmed with other previous studies. Moreover, oral cryotherapy was easy to use and decrease the incidence of oral stomatitis without interference the efficacy of chemotherapeutic drugs. Therefore, oncology nurses should apply additional oral cryotherapy in the routine care for the children receiving chemotherapy with ALL.

VIII. Conclusion

The results of this study revealed that providing oral cryotherapy had significant effects on the chemotherapy induced oral stomatitis. It can be concluded that oral cryotherapy is non-pharmacological and simple approach in preventing oral stomatitis caused by chemotherapy among the children population with ALL. Although oral cryotherapy is newly method to apply as preventive strategy in the Myanmar context, this method did not provide any painful feelings and could not destruct the chemotherapy regimen as side effect. Therefore, oncology nurses can apply this method effectively to prevent oral stomatitis.

IX. Recommendations

According to the evidence of this study, the following recommendations are suggested: standardized oral care including daily oral assessment should be provided before chemotherapy to ensure healthy oral condition; oral assessment tools should be relevant to Myanmar context; oral cryotherapy should be used as evidence based practice in preventing oral stomatitis for the children with ALL receiving chemotherapy at every phases; should be include in routine care for the children receiving chemotherapy; oncology nurses should perform the awareness raising activities regarding the benefits of oral cryotherapy; oncologists and oncology nurses should collaborate to formulate and develop the standard operating procedure guidelines regarding the use of the oral cryotherapy; nurse researcher and researchers in other fields should conduct further studies relating oral cryotherapy with larger sample sizes, different settings, and different approaches to strengthen the evidence of oral cryotherapy on prevention of chemotherapy induced oral stomatitis.

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