

EFFECTIVENESS OF FLAVORED ORAL CRYOTHERAPY ON THE PREVENTION AND MANAGEMENT OF STOMATITIS INDUCED BY CHEMOTHERAPY

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Abstract

Background: Stomatitis is probably the most prevalent, debilitating complication of cancer treatments particularly chemotherapy. **Aim:** This study aimed to examine effectiveness of flavored oral cryotherapy on the prevention and management of stomatitis induced by chemotherapy. **Method :** A quasi experimental design was conducted on a purposive sample of 46 children from both gender with cancer and undergoing chemotherapy who attended the pediatric outpatient clinics and in-patient pediatric oncology department in Oncology Center at Mansoura University and their age from 6-18 years, newly diagnosed with cancer and in induction stage of chemotherapeutic protocol, had a healthy oral mucosa and treated with methotrexate, Adriamycin or 5-Fluorouracil. **Tools:** A structural interview questionnaire sheet about characteristics, clinical data and oral health status of children and oral assessment guide tool (OAG). **Result:** More than half of children in flavored cryotherapy had healthy oral cavity while nearly two third of them had sever stomatitis at 14th day. **Conclusion:** Using flavored oral cryotherapy lead to healthier oral mucosa and lower stomatitis score compared to using only mouthwash (chlorhexidine). **Recommendations:** Provide in-services, up to date, regular training programs to improve nurses' knowledge and practices regarding the use of flavored cryotherapy and mouthwashes as routine care for children treated with chemotherapy **Keywords:** Chemotherapy, Children, Flavored Cryotherapy, Stomatitis

Introduction:

The oral cavity is highly susceptible to direct and indirect toxic effects of chemotherapy and ionizing radiation. The most common oral complications related to cancer therapies are stomatitis, infection, salivary gland dysfunction, taste dysfunction, and pain. Moreover, stomatitis is considered the most common debilitating and serious non-hematological complication of cancer treatment with an incidence rate of 40-100%, depending on the type of malignancy, chemotherapy regimen, chemotherapeutic drug type, age of patient, neutrophil count, and level of oral care (Hashemi, Bahrololoumi,

Khaksar, SaffarzadehandNeamatzade, 2015).

Stomatitis is an inflammation of the oral mucosa that may include the cheek, lips, tongue, palate and floor of the mouth. It can occur in any region of the mouth but more frequently affects non-keratinized regions such as the buccal mucosa, soft palate and the floor of the mouth. Stomatitis begins on the 3rd to 5th day from starting chemotherapy with a peak on the 7th to 14th day after chemotherapy and normally lasts for 3 weeks (Rashad, 2015).

Consequently, many of pharmacological and non-

pharmacological methods have been tested for its effect on elimination of chemotherapy-induced stomatitis. Chlorhexidine is one of the most antimicrobial agent that is widely used in clinics to treat oral mucositis and candida infections in the mouth, as it is a broad-spectrum antiseptic agent known by its effective action both on Gram-positive and Gram-negative bacteria as well as on fungi. The antibacterial effect of chlorhexidine continues for 12 hours. For this Chlorhexidine has a unique role in many oral care protocols for prevention of oral mucositis (Abdel Moneim, Guerra-Librero, Florido, Shen and Fernández-Gil, 2017).

On the other hand, cryotherapy is a non-pharmacological methods that used for reducing the occurrence of chemotherapy-induced stomatitis which using the local cooling of tissues for treatment and prophylaxis purposes. It is reported that, cryotherapy induce local vasoconstriction causing reduce of oral mucosal blood flow. So, it reduces the amount of blood containing chemotherapy drugs from reaching the mouth with a consequent decrease the direct toxicity. Additionally, cryotherapy has been shown to reduce the incidence of oral mucositis by 50% following intravenous administration of chemotherapy (Riley et al., 2015).

Moreover, clinical researches have shown that, honey help in destroying pathogens causing food-borne illness such as Escherichia coli and Salmonella, as well as, it help in fighting bacterial strains causing resistance to antibiotics and allows antibiotics to make its effect. Furthermore, basil plant that known as "the mother medicine of nature" help in decreasing inflammation, pain and can repair cells damaged by oxidation and radiation and has the potential to destroy

pre-cancerous lesions and tumor as well as inhibits the multiplication, migration and invasion of cancer cells and will also induce apoptosis (programmed cell death of tumors) (Mishra and Nayak, 2017).

Pediatric nurses who are responsible for maintaining safety and high quality of life for the children and their family, play an active role in the prevention and management of chemotherapy induced stomatitis through understanding of the children's condition, goal of therapy, drug dose, schedule, and potential side effects as well as, using the appropriate diagnostic tools for the identification of stomatitis, providing care to promote proper healing. Also, they should provide health education for children and their family about proper mouth care and preventive measures for oral mucositis. Therefore, the nursing team needs to be regularly involved in continuing evidence based education, to keep up-to-date about clinical practice grounded in scientific base (Manzi, Silveira and Reis, 2016).

Therefore, the aim of the Study is to examine effectiveness of flavored oral cryotherapy on the prevention and management of stomatitis induced by chemotherapy.

Research Hypothesis

Children who will receive flavored oral cryotherapy with honey and basil may have healthier oral mucosa and lower stomatitis score compared to children using mouthwash (chlorhexidine).

Subjects and Method

Research Design

A quasi experimental design was used to accomplish this study.

Study Setting

This study was conducted at pediatric outpatient clinics and in-patient

pediatric oncology department in Oncology Center at Mansoura University

Study subjects:

A simple random sample of 46 children from both gender with cancer and undergoing chemotherapy who attended the previously mentioned setting and their age from 6-18 years, newly diagnosed with cancer and in induction stage of chemotherapeutic protocol, had a healthy oral mucosa and treated with methotrexate, Adriamycin or 5-Fluorouracil were included in this study.

Tools of data collection:

Two tools were used in this study.

Tool I: A structural interview questionnaire sheet

A structural interview questionnaire sheet was designed, adjusted and prepared by the researcher after reviewing the related literature and the modifications of study supervisors. It consisted of five parts:

Part I: Characteristics of the studied children:

This part included data about; age, sex, residence, birth order and educational level of studied children.

Part II: studied children clinical data:

This part included data about; diagnosis, chemotherapy type, duration of chemotherapeutic session, side effect of chemotherapy, whether the child suffered from any other medical problem, whether the child take other medication beside chemotherapy.

Part III: Children's oral health status:

This part included data about; mouth cleanliness, the time child clean his/her mouth, method used for oral care and if the child suffering from any oral problems

Part IV: Sucking honey and basil ice cubes:

This part included data about; how the children suck ice cubes, duration of sucking ice cubes, if the child suffering from any problems related to sucking flavored ice cubes

Part V: mouthwash with chlorhexidine:

This part included data as; is the child use chlorhexidine as mouthwash, how many time the children use chlorhexidine as mouthwash daily, when the child use chlorhexidine as mouthwash, duration of washing mouth by chlorhexidine, is the child suffering from any problems related to chlorhexidine usage.

Tool II: Oral assessment guide tool (OAG):

Oral assessment guide (OAG) adopted from **Eilers, Berger and Petersen (1988)** was used to evaluate the condition of oral cavity and the degree of stomatitis for children. The tool consists of eight items: voice, swallow, lips, tongue, saliva, mucous membranes, gingiva and teeth or dentures.

Scoring system:

Oral assessment guide covered 8 items: voice, swallow, lips, tongue, saliva, mucous membranes, gingiva and teeth or dentures. The total scores equal 24 marks and was categorized as the following:

- Score from 1 to 8 indicates healthy oral cavity,
- Score from 9 to 16 indicates moderate stomatitis
- Score from 17 to 24 indicates severe stomatitis.

II - Operational design

1 -Preparatory phase

This phase included a review of past and current related literature and studies, using available appropriate books, periodicals, magazines, and articles to get acquainted with various aspects of the study research develop the

study tools. The structured interview questionnaire was developed in an Arabic language by the researcher after reviewing of the related literature, then revised and adjusted by supervisors. The content validity of the study tools was assessed and revised by a panel of 5 experts in the field nursing from Mansoura faculty of nursing and no modifications were done. The internal consistency of the developed tool was tested by using Cronbach's alpha coefficient and the tool was reliable as $r = 0.87$. as well as, the internal consistency of the adopted tools (OAG) (tool II) was tested and it was ($r = 0.912$).

2 - Exploratory phase:

a) Pilot study:-

A pilot study was carried out on a total of 10% of the total subject's size (5 children) according to the criteria of selection before starting the data collection and they were selected randomly. There was no modification has been done so, they were included among the study total sample

Filed work:

Data collection period:

Data collection extended over a period of eight months started from the 1st of January, 2019 to 30th of August, 2019. The researcher attended 6 days per week, from 8 am to 3 pm. The researcher started by introducing herself to the study subjects, and giving them a brief idea about aims and nature of the study as well as method of data collection to obtain their oral approval to participate in the study. The researcher filled the questionnaire sheet by herself.

• Study framework:

The framework of the study was carried out according to 4 phases as the following:

Phase 1: preparatory phase:

- Each child and his/her mother was interviewed individually before using flavored cryotherapy or chlorhexidine in order to collect the needed data base line using the study tool (I) part(I). It was continued for 30 minutes
- Oral Assessment Guide (tool II) was done for each child included in the study before starting intravenous chemotherapy session to ensure that he/she has a healthy oral mucosa. It took within 7-10 minutes

Phase 2: planning phase

- All the study sample was be treated with the same chemotherapy regimens (methotrexate, adrimycine and 5-FU) and they were divided into two equal groups (23 child in each group) and the children who was meet the inclusion criteria was selected randomly, as they were arranged in a list according to their admission to the study setting and then selecte odd number to be in first group (A) and the and the even number to be in second group (B).

Phase 3: implementation phase

- The first group (A) take chlorhexidine 0.12% mouthwash and children were be instructed to swirl it around in the mouth for 30 second, twice daily, from the first day of taking chemotherapy to days 21. It was without alcohol and with taste additives. . It was take 5 mintues to teach child this technique
- The researcher who brought the needed chlorhexidine and save it in the refregator in the inpatient ward. The researcher wrote each child name on his mouthwash bottle and told all the nurse in the ward and also the children's mother about that.

- The second group (B) take ice cubes that was be made by the researcher from honey and basil five minutes before chemotherapy session, continuing half an hour throughout the session and for additional thirty-five minutes after completion of chemotherapy session. The children were instructed to move the ice cubes in their mouth constantly during session. Children who were not tolerated sucking the ice cubes for whole planned duration, were allowed to suck for an intermittent duration but, take into consideration to keep mouth cavity cool as can as possible. It took 5 mintues to teach child this technique and all phases were done within 75 minutes.

Phase 4: evalaution phase:

- Oral Assessment Guide (tool II) was used to follow up the children's mouth as the following at 3rd, 5th,7th, 14th, and 21th day after chemotherapeutic session. As well as, each child in group (A) was monitored to assess his/her compliance with chlorhexidine as in Part (V) in tool (I). The researcher taught each child to count from 1 – 30 during washing his mouth by chlorhexidine.

III - Administrative design.

An official approval was obtained from Research Ethics Committee of the Faculty of Nursing to carry out the study. An official letter was submitted from the Dean of Faculty to the directorof hospital and head nurse of the outpatient clinics and inpatient department of oncology center at Mansoura University to obtain an approval to carry out the study after giving an explanation to the aim and nature of the study.

Ethical considerations:

An informed oral consent was

obtained from mother for their children participation after explaining the purpose, benefits, risks and procedure of the study. Anonymity and confidentiality of data was assured and was used only for research purposes. Participants were informed that their participation in the study is voluntary and they had the right to withdraw at any time freely without any responsibilities or any affect on their care.

I V- Statistical design:

Data were analyzed with SPSS version 24. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Quantitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. When more than 25% of the cells have expected count less than 5, Fisher exact test was used. Continuous variables were presented as mean \pm SD (standard deviation) for parametric data and Median for non-parametric data. The two groups were compared with *t* test (parametric data) and Mann–Whitney test (non parametric data).Analysis Of Variance (ANOVA test) used for comparison of means of more than two groups (parametric data) and Kruskal Wallis Test for comparison of means of more than two groups (non parametric data). Pearson correlation used for correlation between continuous parametric data while spearman correlation to correlate between continuous non- parametric data.

Result

Table (1) revealedthat, the highest percentages of studied children in flavored cryotherapy (G1), Chlorhexidine (G2) groups were male (60.9%& 52.2%) respectively,

Table (2): clarified that, most of the children in flavored cryotherapy (G1)

and chlorhexidine (G2) groups were diagnosed as leukemic and treated with Adriamycin for 4 hours per session (69.6% & 56.5%) respectively.

Figure (1): revealed that, all (100%) the studied children at all groups had healthy oral cavity at the first day before starting the chemotherapeutic session. While on the 5th day from chemotherapeutic session 47.8% of them had a healthy oral cavity in flavored cryotherapy with honey and basil group compared to 65.2% of them had moderate stomatitis in chlorhexidine group. As well as, 87% of studied children had a healthy oral cavity in flavored cryotherapy with honey and basil group 21.7% of them had severe stomatitis in chlorhexidine group at 21st day

Table (3); It is revealed from this table that, the mean \pm S.D of flavored cryotherapy (G1) and chlorhexidine (G2) and was identical (8.00 \pm .00) on the first

day, and this value begun to increase from the 3rd day to (8.65 \pm 0.49 & 8.52 \pm 0.51) respectively through 7th day (15.09 \pm 3.41 & 10.83 \pm 3.19) respectively and reach to the maximum at 14th day (15.78 \pm 4.86 & 12.35 \pm 4.70) then decreased at 21st day (10.43 \pm 4.62 & 9.00 \pm 3.16) respectively in chlorhexidine group (G2) and flavored cryotherapy (G1).

Table (4); It is clear from this table that, there were statistical significance relationship between severity of stomatitis regarding children's diagnosis and prescribed chemotherapeutic agents as p value = .004 and .002 respectively

Table (5); It is revealed from this table that, there were statistical significance relationship between children's diagnosis and prescribed chemotherapeutic agents and severity of stomatitis as p value = 0.000 and 0.001 respectively

Table (1): Number and percentage distribution of studied children according to their characteristics (n= 46)

characteristics		Flavored cryotherapy (G1) (23)		Chlorhexidine (G2) (23)	
		N	%	N	%
Gender	Male	14	60.9	12	52.2
	Female	9	39.1	11	47.8
Age	6:>9	5	21.7	9	39.1
	9:>12	8	34.8	4	17.4
	12:>15	6	26.1	7	30.4
	15:18	4	17.4	3	13
Education	primary	16	69.6	13	56.5
	preparatory	7	30.4	7	30.4
	Secondary	0	0	3	13

Table (2): Number and percentage distribution of studied children according to their clinical data (n= 46)

Clinical data		Flavored cryotherapy (G1) (23)		Chlorhexidine (G2) (23)	
		N	%	N	%
Diagnosis	Leukemia	16	69.6	13	56.5
	Sarcoma	3	13	7	30.4
	Lymphoma	4	17.4	3	13
Prescribed Chemotherapeutic agents	Methotrexate	4	17.4	7	30.4
	Adriamycin	16	69.6	13	56.5
	Fluorouracil	3	13	3	13
Chemotherapeutic session duration	2 hours	3	13	3	13
	4 hours	16	69.6	13	56.5
	6 hours	4	17.4	7	30.4
* Side effects of chemotherapy	Skin rash	3	13	2	8.7
	Nausea, vomiting, anorexia, weight loss, alopecia	23	100	23	100

*More than one answer may be presented in the same child.

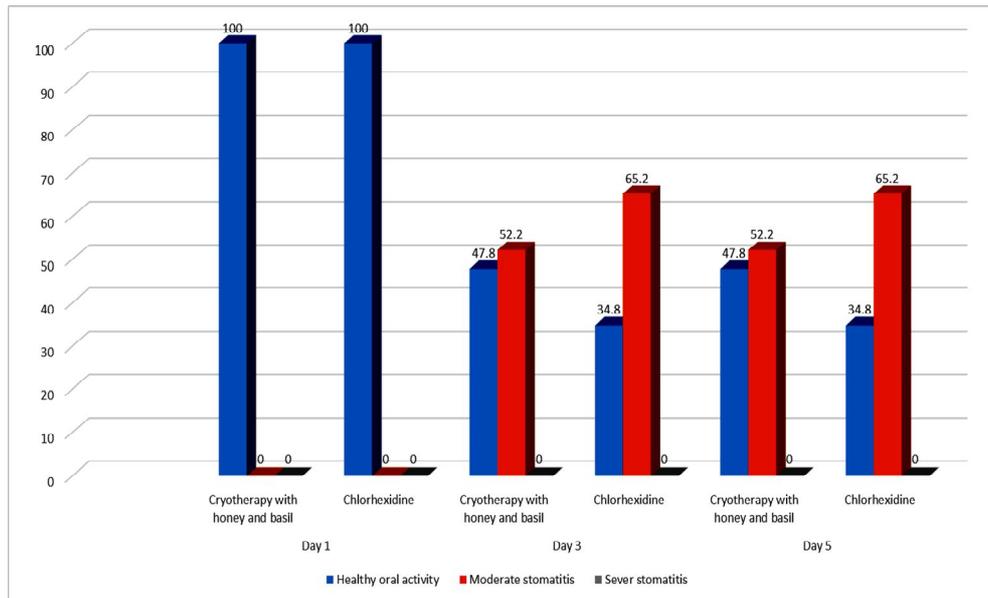
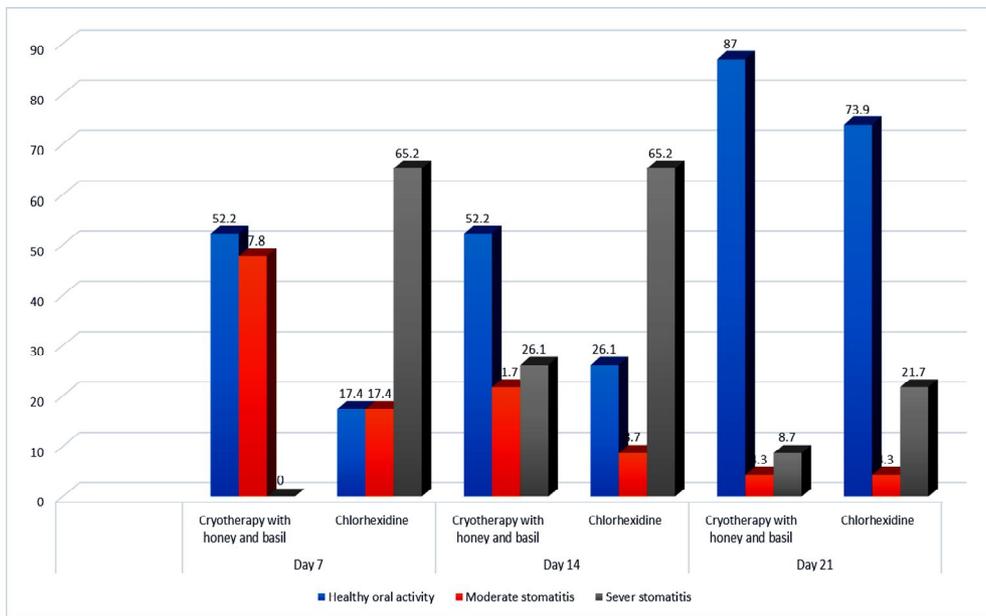


Figure 1: percentage distribution of stomatitis induced by chemotherapy among studied groups by using oral assessment guide



Cont. Figure 1: percentage distribution of stomatitis induced by chemotherapy among studied groups by using oral assessment guide

Table (3): Mean score and standard deviation of stomatitis severity during days of assessment among studied groups (n= 69)

Days of OAG	Interventions used	Mean± S.D.	Z1	p	Z2	p	Z3	p	X2	P
Day 1	Flavored cryotherapy	8.00± .00	264.500	1.000	264.500	1.000	264.500	1.000	.000	1.000
	Chlorhexidine	8.00± .00								
Day 3	Flavored Cryotherapy	8.52± 0.51	230.000	0.374	126.500	.001	92.000	.001	22.667	.000
	Chlorhexidine	8.65± 0.49								
Day 5	Flavored Cryotherapy	8.52± 0.51	140.000	0.003	149.500	0.003	100.000	.000	22.207	.000
	Chlorhexidine	12.57± 3.41								
Day 7	Flavored Cryotherapy	10.83± 3.19	82.000	0.000	150.00	0.002	50.000	.001	35.140	.000
	Chlorhexidine	15.09± 3.41								
Day 14	Flavored Cryotherapy	12.35± 4.70	124.000	0.002	138.000	0.001	69.000	.000	30.058	.000
	Chlorhexidine	15.78± 4.86								
Day 21	Flavored Cryotherapy	9.00± 3.16	228.500	0.252	230.000	0.077	195.500	.000	6.877	.022
	Chlorhexidine	10.43± 4.62								

Table (4); Relationship between clinical data of the studied children receiving flavored erythrotherapy and severity of stomatitis in relation to oral assessment guide (N=23):

Clinical data	Healthy oral cavity						Moderate stomatitis						Sever stomatitis						Test of Sig.									
	N			%			N			%			N			%			* X2			P						
	D	D	D	D3	D7	D21	D	D	D	D3	D7	D21	D	D	D	D3	D7	D21	D	D	D	D3	D7	D21				
	3	7	21				3	7	21																			
Diagnosis																												
Leukemia	7	7	14	63.6	58.3	70	9	9	1	75	81.8	100	0	0	1	0	0	0	50									
Sarcoma	1	3	3	9.1	25	15	2	0	0	16.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.707
Lymphoma	3	2	3	27.3	16.7	15	1	2	0	8.3	18.2	0	0	0	1	0	0	0	50									
Prescribed chemotherapeutic agents																												
Methotrexate	3	2	3	27.3	16.7	15	1	2	0	8.3	18.2	0	0	0	1	0	0	0	50									.707
Adriamycin	7	7	14	63.6	58.3	70	9	9	1	75	81.8	100	0	0	1	0	0	0	50									
Fluorouracil	1	3	3	9.1	25	15	2	0	0	16.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Chemotherapeutic session duration																												
2 hours	1	3	3	9.1	25	15	2	0	0	16.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
4 hours	7	7	14	63.6	58.3	70	9	9	1	75	81.8	100	0	0	1	0	0	0	50									.707
6 hours	3	2	3	27.3	16.7	15	1	2	0	8.3	18.2	0	0	0	1	0	0	0	50									
* side effects of Chemotherapy																												
Skin rash	1	1	0	8.3	8.3	0	2	2	1	14.3	14.3	50	0	0	2	0	0	0	66.7									
Nausea, vomiting, anorexia, weight loss, alopecia	11	11	21	91.7	91.7	100	12	12	1	85.7	85.7	50	0	0	1	0	0	0	33.3									.444

* Fisher's Exact Test

* More than one answer may be presented in the same child.

Discussion

The oral mucositis is a crucial adverse effect of cancer treatment that influence persons' quality of life, co morbidity and death rate. Different prophylactic agents are examined and suggested to manage these adverse effects (**Soliman, 2019**). Several studies reported that, mouthwashes as chlorhexidine that has beneficial action against candida, some viral, fungal and bacterial infection as well as, flavored oral cryotherapy with honey and basil have a useful effect in decreasing the development of oral mucositis induced by chemotherapy (**Mishra and Nayak, 2017**). Therefore, evaluation the effectiveness of flavored oral cryotherapy versus mouthwash on the prevention and management of stomatitis induced by chemotherapy is of utmost importance to decrease morbidity and mortality rate among children undergoing chemotherapy.

As regards characteristics of the studied subjects and their clinical data, the present study found that, more than half of studied children in flavored cryotherapy (G1) and Chlorhexidine (G2) were male (**Table 1**). This findings was in an agreement with **Williams, Richardson, Marcotte, Poynter and Spector (2019)** who conducted on a study about "Sex ratio among childhood cancers by single year of age" and reported that, 53% of their studied children were male, and the male sex was positively associated with most types of cancer among children and adolescent. From the researcher point of view, the relationship between childhood sex and incidence of cancer remain largely unexplored but **Dunford , Weinstock and Savova (2017)** reported that, it may be due to the

difference in the biologic mechanisms of both sex such as genetic factors as germline variation and gene expression on the X and autosomal chromosomes, as well as, presence of a sex responsive gene near to the ABO blood group gene locus on chromosome '9' which relatively protects group O among girls against many types of cancer particularly, leukemia also, immune responses and pubertal hormone profiles and the corresponding growth rates that may contribute to the increased cancer incidence among males.

The findings of this study cleared that, all children had a healthy oral cavity before administration of chemotherapy and at 3rd day from chemotherapeutic session about half of them who suck flavored ice cubes with honey and basil had healthy oral cavity (**Figure 1**). This finding was consistent with **Rashad (2015)** who mentioned on a study about "Effect of cryotherapy on the occurrence of stomatitis induced by chemotherapy among children with bone tumors in Egypt" that, at 3rd day majority of children who sucked ice cubes had healthy oral cavity.

Moreover, the result of the current study pointed out that, more than half of studied children in flavored cryotherapy group had healthy oral cavity at 7th and 14th day (**Figure 1**). This result was in the same line with **Mishra and Nayak (2017)** who reported that, the majority (85%) of children who suck ice cubes of honey and tulsi had a healthy oral cavity on 7th day and 14th day from chemotherapy session.

This findings of the present study illustrated that, **nearly two third of studied children in chlorhexidine group had sever stomatitis at 7th and 14th day from chemotherapeutic**

session while no one of them at 7th day and about one quarter of them at 14th day in flavored cryotherapy groups had sever stomatitis at the same day (Figure 1). This result was in the same track with Chaveli-López and Bagán-Sebastián (2016) who conducted a study about “Treatment of oral mucositis due to chemotherapy” and stated that, children used ice cubes sucking were less frequently had grade III or sever oral mucositis at 7th and 14th than who used chlorhexidine.

Concerning, relationship between clinical data of the studied children receiving flavored cryotherapy and severity of stomatitis in relation to oral assessment guide (Table 4), the present study indicated that, there was a statistical significance relationship between children's prescribed chemotherapeutic agents and the severity of stomatitis. This result was in agreement with Peterson(2013) who conducted a study on “New Strategies for Management of Oral Mucositis in Cancer Patients” and mentioned that, the type of chemotherapeutic agents that are used, the specific dose, route, and frequency of administration and whether the chemotherapy given as monotherapy or in combination with other agents and modalities of treatment significantly affect the incidence and degree of stomatitis.

Conclusion:

Using flavored oral cryotherapy with honey and basil lead healthier oral mucosa and lower stomatitis score compared to children using mouthwash (chlorhexidine), particularly for chemotherapeutic drugs that have short plasma half-life such as methotrexate, adriamycin and fluorouracil.

Recommendation:

Provide in-services, up to date, regular training programs to improve nurses' knowledge and practices regarding the use of flavored cryotherapy and mouthwashes as routine care for children treated with chemotherapy.

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