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Effect of Cryotherapy on the Occurrence of Stomatitis Induced by Chemotherapy among Children with Bone Tumors in Egypt

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Abstract
Stomatitis has been shown to occur closer to fourty percent in solid tumor children receiving chemotherapy. Cryotherapy is an alternative method of preventing stomatitis associated with chemotherapeutic drugs. This study aimed to evaluate the effect of oral cryotherapy on the occurrence of stomatitis induced by chemotherapy among children with bone tumors. A quasi-experimental design was utilized on a convenient sample of 60 children with bone tumors, thirty of them followed the hospital routine care (control group) and other thirty sucked ice cubes (study group) before inducing chemotherapy session for five minutes to half an hour during session and thirty five minutes after session. Both groups were treated with the following chemotherapy drugs: Adriamycin and Methotrexate. This study was conducted at the National Cancer Institute (NCI), Cairo, Egypt. Oral assessment guide (OAG) was used prior, 3rd, 4th and 5th days post intravenous chemotherapy administration during induction phase. Results revealed that no significant difference was detected in the mean total scores of both group prior to chemotherapy administration while it decreased significantly at the third, fourth and fifth days post chemotherapy for children who received oral cryotherapy than do not received. Children who received oral ice cubes had healthier oral cavity than who did not receive. It was concluded that oral cryotherapy reduces the severity of stomatitis induced by chemotherapy. Oral cryotherapy must be involved in the routine care for a child who receiving chemotherapy was recommended.
Keywords: Oral Cryotherapy, Stomatitis, Chemotherapy, Bone Tumors, Children

1.Introduction:

Stomatitis is an inflammation of the oral mucosa which 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 (Cheng & Chengo, 2009). Stomatitis begins on the 3rd - 5th day from starting chemotherapy with a peak on the 7th -14th day after chemotherapy and normally lasts for 3 weeks (Eilers &Milion, 2012). Stomatitis is caused by direct effect of chemotherapy by interfering with actual cell production, maturation and replacement and indirectly due to bone marrow depression during which neutropenia and thrombocytopenia lead to increased risk of bleeding and infection (Eilers, 2004).

Alterations of normal oral health influence quality of life through changes that affect these activities (Thurgood, 2013). Oral stomatitis is a common complication of cancer therapy. Stomatitis results from damage to the mucosal epithelium after delivery of chemotherapy or radiation designed to treat the cancer (Lilleby, etal, 2006). Under normal conditions, oral mucosa and normal saliva activity are two important barriers that prevent invasion by microorganisms. Nevertheless, in the presence of chemotherapeutic drugs this barrier becomes disrupted.

Stomatitis disrupts the function and integrity of the oral cavity, which affects functional status and quality of life (Gold berg etal, 2004) and (Svanberg, Ohrn & Birgegard , 2010). Stomatitis is linked to clinical morbidity, pain, malnutrition, and local and systemic infections (Harrism ,Eilers & Harriman,2008). Treatment delays and dosage adjustments can also occur resulting in dose reductions in subsequent cycles of chemotherapy or even discontinuation of treatment. Dose reductions have been seen in 60% of patients and discontinuation of regimens in about 30% (Sonis, Elting & Keefe, 2004).

The type of chemotherapeutic agents that are used, the specific dose, route, and frequency of administration and whether the chemotherapy is given as monotherapy or in combination with other agents and modalities of treatment significantly affect the degree of stomatitis (Peterson, 2006)).Also previous exposure to chemotherapy agents increases the risk of stomatitis (Naidu.et.al,2004). The prevalence of stomatitis has been

shown to occur closer to 40 % in solid-tumor children receiving chemotherapy (Wohlschlaeger, 2010). Of these, 5% to 15% have OAG grades 2 to 3 stomatitis (Peterson, 2006). Chemotherapy drug regimens such as methotrexate (MTX) have rate of (20%–50%), and other antimetabolites which have 20%–60% rates of alimentary tract mucositis, in particular stomatitis (Stokman.et.al, 2006) and (Elating,etal., 2007).

According to the U.S.A Surveillance, Epidemiology and End Results Program (SEER), osteosarcomas contribute 36% of all types of bone cancer among children, followed by chondrosarcom as and Ewing's sarcomas with around 30% and 16% respectively (Linabery & Ross, 2008). In Egypt, malignant bone tumors among children ranked number three after leukemia and lymphoma constitute 7.87% of tumors in adolescent age group. Osteosarcoma was the most common primary malignant bone tumors constituting 47.75% followed by Ewing sarcoma 17.57%, chondrosarcoma14.86% and lymphoma 9.01% among children (Mokhtar, Gouda & Abdel-Moneam , 2010).

The primary treatment of bone tumors in children is chemotherapy (Kyle, 2008). Chemotherapy is the use of powerful and toxic drugs to attack cancer cells. It destroys cancer cells by stopping them from growing or multiplying. Healthy cells can also be harmed, especially those that divide quickly (Rebecca, 2009).

Children with newly diagnosed osteosarcoma were treated at NCI, CU. with osteosarcoma protocol (OS99) that incorporated polychemotherapy and aggressive surgery. Therapy comprised 12 intensive cycles of chemotherapy administered every 3 weeks with hematopoietic growth factor support for a total of 35 weeks. After 4 cycles of neoadjuvant chemotherapy, surgery for local control was done, mostly by a limb-sparing procedure, and followed by 8 additional cycles of chemotherapy**.** For Ewing sarcoma it consisted of 3 phases: Induction, local control and maintenance. Induction phase consisted of two courses of ifosfamide and etoposide alternating with one course of vincristine, Adriamycin and cyclophosphamide. Maintenance therapy consisted of courses of ifosfamide and vepeside alternated with vincristine, adriamycin and cyclophosphamide until the end of chemotherapy (Abd Elrahman,etal, 2010).

Management of oral complication of cancer therapy includes identifications of high risk populations, patients education, initiation of pretreatment interventions, and timely management of lesions. Primary assessment of the oral status and stabilization of oral disease prior to cancer therapy are critical to overall patient care. This care should be both preventive and therapeutic as indicated to minimize risk for oral and associated systemic complication (Cheng, Molassiostis, Chang&Wai, 2011).

Several methods have been proposed for preventing chemotherapy-induced oral complications The revision of the Multinational Association of Supportive Care in Cancer, 2007 (MASCC) guideline has recommendations for the use of palifermin for oral mucositis (OM) associated with stem cell transplantation, mifostine for radiation proctitis and cryotherapy for mucositis associated with high-dose melphalan(Keefe.et.al,2007). In addition, there have been several reports of reduced chemotherapy-induced OM by cryotherapy (Rankin &Jones, 2009).

Oral cryotherapy is the application of ice cubes or ice-cold water to the mouth. Oral cryotherapy for chemotherapy-induced stomatitis requires that children suck on ice chips before, during, and after infusions of mucotoxic drugs (Harris , Eilers & Harriman,2008). The theory underlying oral cryotherapy is that ice can constrict the blood vessels of the oral cavity membranes, therefore decreasing exposure of the oral mucosa to mucotoxic agents (Nikoletti , Hyde, Shaw & Myers ,2005).Oral cryotherapy is an alternative method of preventing stomatitis associated with chemotherapy agents that have a short half-life in the blood. It is a well-validated, simple, cheep, and effective approach for the prevention of stomatitis associated with bone tumors (Smyth, 2009).

The children will instruct to move the ice cubes in their mouth constantly and not to keep them stationary (Worthington & Clarkson, 2010). Oral cryotherapy was initiated five minutes before chemotherapy and cryotherapy was maintained depending on the characteristics of the chemotherapy protocol and the duration of infusion of various chemotherapeutic agents. Small ice cubes kept in the refrigerator before chemotherapy was given to the patient in succession without waiting for them to melt (Sherife, 2008).

Cryotherapy is the most conventional and easy-to-use preventive method, at least for 5-FU-based bolus therapy, and appears to have implications for other chemotherapy regimens as well, such as edatrexate and melphalan (Sideras, Loprinzi & Foote, 2008). Studies have provided support for the use of cryotherapy with high-dose melphalan. (Aisa, et.al, 2005) According to a report of the ESMO Guidelines Working Group, oral cryotherapy (30 min) is recommended for the prevention of OM in patients receiving bolus 5-FU chemotherapy and 20-30 min of oral cryotherapy is suggested to decrease mucositis in patients treated with bolus doses of edatrexate (Tartarone, etal, 2005) For oral cryotherapy, the effectiveness is limited to single chemotherapy agents that have a short half-life. The majority of evidence to date is for 5-FU and high-dose melphalan. To date, this simple method has not been used in combination chemotherapy regimens such as5-FU with leucovorin (MAYO); the combination of cyclophosphamid, Adriamycin and 5-fluorouracil (CAF); or the combination of cyclophosphamid, methotrexate and fluorouracil (Mori, 2006).

According to the results of systematic reviews by Worthington et al. in 2007 and 2010, several interventions have been found to be somewhat beneficial at preventing or reducing the severity of stomatitis associated with cancer treatment. However the strength of the evidence was variable and implications for practice include consideration that the benefit of cryotherapy may be specific for certain cancer types and treatments. According to Worthington, "There is a need for well-designed and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent (Worthington,Clarkson & Eden,2007)and(Worthingt,et.al,201) . There is a lack of studies that report on the use of cryotherapy in children who undergo single or combined chemotherapy regimens in Egypt. In addition, in the nursing literature related to mucositis management, standard treatment and maintenance practices for mucositis prevention are quite limited. Yet, as the primary caregivers for the patients, nurses should have a central position in the prevention and management of mucositis.

The pediatric oncology nurse has an important role in the prophylaxis of chemotherapy induced stomatitis through understanding of the patient's condition, goal of therapy, drug dose, schedule, administration principles, and potential side effects. Additional nursing management includes monitoring responses to therapy, reassessing and documenting information, ongoing patient teaching oral hygiene and care regimens (Coulson, 2010).

2.Significance of the study:

Stomatitis may decrease the effectiveness of treatment as well as decrease the quality of life in the pediatric oncology patient. Poor oral health has significantly negative effects on systemic health so the oncology pediatric nurse has important role in preventing oral stomatitis for cancer children to reduce the impact of oral microbial flora, reduce cancer therapy related to stomatitis, and maintain nutritional status and to prevent soft tissue infections that may have systemic sequel. One intervention that has been proven to be successful in preventing oral stomatitis is cryotherapy or rapid cooling of oral cavity using ice.

3. Aim of the study:

This study aimed to:

- Evaluate the effect of oral cryotherapy on the occurrence of stomatitis induced by chemotherapy among children with bone tumors.

4.Research Hypothesis:

1. Children who will receive cryotherapy will have healthier oral cavity compared to children in controlled group.
2. Children who will receive cryotherapy will have lowest score of oral stomatitis compared to children in controlled group.

5.Subject and Methods:

5.1 Research design:

A quasi-experimental research design was utilized to achieve the aim of the study.

5.2 Subject:

A convenient sample of 60 children undergoing chemotherapy was included in the study. It was divided equally to two groups, thirty of them followed the hospital routine care (control group) and other thirty sucked ice cubes (study group) before chemotherapy session for five minutes to half an hour during and thirty five minutes after chemotherapy session. Both groups were treated with the following Chemotherapy regimens: Adriamycin and methotrexate.

-All children met the following inclusion criteria: both sexes, age ranged from 6-18 years, having healthy oral mucosa, having bone tumor for the first time and receiving primary line of chemotherapy. Children having neutropenia defined as absolute neutrophil count (ANC) < 1500 / mm3 had excluded.

5.3 Setting:

This study was carried out in the pediatrics out patient's clinics and Oncology Department at the NCI, Cairo University (CU),that provides care for all children from all over Egypt.

5.4 Tools for data collection:

Two tools were used for data collection:

A- **A structured interview questionnaire sheet** was constructed by the researchers after reviewing the relevant literature. It included children characteristics as age, sex, educational level, and diagnosis and chemotherapy drug type. Lab investigations assessed before and after induction of chemotherapy.

B- **Oral assessment guide (OAG) tool** that was developed by Eilers et al, (1988) to evaluate the condition of oral cavity and the degree of stomatitis for children. The tool assesses eight items: swallow lips and corner of the mouth, tongue, saliva, mucus membrane, voice, gingivae and teeth. Oral assessment guide 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.

5.5 Validity and reliability:

- Tool was submitted to panel of five experts in the field of Pediatric oncology and pediatric nursing to test the content validity. No modifications were done.
- Reliability test was done using Cronbach's alpha for first tool was 6.5 and second tool 9.6.

1. Pilot study:

A pilot study was carried out on 10% of the total sample (6 children) to test study tools in terms of their clarity, applicability, time required to fill in them and accordingly no modifications were done. Subjects who shared in the pilot study were included in the sample.

2. Data collection procedure:

An official approval was obtained from NCI administrators of the study setting where a clear explanation was given about the nature, importance and expected outcomes of the study. The filed work was carried out from the first of December 2012 to the end of May 2013(6-months). Written formal consent obtained from parents/caregiver of children.

For control group: each child was interviewed individually in the individual room of Out and inpatient Pediatric Oncology Departments before chemotherapy session to fulfill the questionnaire sheet. OAG was used four times: 1st day observation before starting intravenous chemotherapy session, 3rd, 4th and 5th day after chemotherapy administration sessions to assess the oral health status. They neither were nor received cryotherapy.

For study group: interview and OAG were used as control group. They were informed about importance of oral cryotherapy then every child was asked to suck ice cubes for five minutes before the beginning of chemotherapy session, continuing 30 minutes throughout session and for additional 35 minutes after completion of intravenous chemotherapy session .This time was determined based on the half- lives of the chemotherapeutic drugs. Children who did not tolerate sucking the ice cubes for whole planned duration (30mintues) were allowed to suck for an intermittent duration (30 minutes).Oral cryotherapy used in this study was prepared in special containers of ice cubes using distilled water.

3. Statistical design:

- Data was analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using either student t-test or Mann-Whitney test (non-parametric t-test). Paired t-test was used to compare two consecutive measures of numerical variables. Reliability of the oral assessment questionnaire was done using Cronbach's Alpha. A p-value < 0.05 was considered significant.

4. Ethical consideration:

Ethical approval was obtained from the relevant Ethics Committee of Faculty of Nursing, Cairo-University to carry out the study**.** Written consent was obtained from parents before data collection. Each child and his/her parent had the freedom to withdraw at any time. Confidentially of data were ensured.

5. Results:

Table (1) Indicated that mean age of children in both groups was nearly equal as (15. 0 $\pm$ 1.64 & 15.4 $\pm$ 1.76 years) with no statistically significant difference. Regarding sex, the highest percentages of both groups were males (56.7%, 60%). The same table revealed that the majority of children in the study and control group diagnosed as osteosarcoma (80% &93.3% respectively) and treated with methotrexate for 6 hours per session while the minority (20% & 6.7% respectively) had Ewing's sarcoma and treated with Adriamycin for 4 hours. No statistically significant differences were detected between both groups as ($P > 0.05$).

Regarding to total scores of oral assessment guide pre and post oral cryotherapy table (2) showed that all children in the study and control groups had healthy oral cavity with no statistically significant differences pre cryotherapy. Concerning 3rd days post cryotherapy, the highest percentage of study group (93.3%) had healthy oral cavity compared to 23.3% of the control group had severe stomatitis .Regarding to 4th day, (70%) of study group had healthy oral cavity compared to 26.7% of the control group had sever stomatitis. As classified in this table, 5th days. (96.7% &46.7%) had moderate stomatitis in the study and control group respectively, and 53.3% of the control group only had sever stomatitis A highly statistically significant differences was detected between the study and control groups in the 3rd , 4th , &5th day as $p< 0.001$.

Table(3) Indicated that the mean total oral assessment scores was a statistically significant different between the study and control group at 3rd, 4th and 5th days post cryotherapy at a significance level as $p< 0.001$.

Table (4) illustrated that at the 3rd day more than half of children (60%) who sucked ice continuously

had healthier oral cavity compared to 33.3% of children who intermittently sucked ice, only about 7% of them suffered from moderate stomatitis with none of them had sever stomatitis. There was statistically significant difference as ($P > 0.05$). While no significant difference was detected at 4^{th} and 5^{th} days.

Table (5) showed that no significant relation between total scores of oral assessment guide at 5^{th} day and child characteristics for both groups as ($P > 0.05$).

Table (1): Percentage distribution of children characteristics of study and control group (n=60)

Child characteristics	Study(N=30)		Control(N=30)		X^2	P
	NO	%	NO	%		
Age(in years): -6-<9 -9-<12 -12-<15 -15-18	 1 3 16 10	 3.3 10 53.3 33.3	 4 3 8 15	 13.3 10 26.7 50	1.23	.152
Mean ± SD	15. 0±1.64		15.4 ±1.76			
Sex : -Male -Female	 17 13	 56.7 43.3	 18 12	 60 40	.069	.793
Diagnosis : Bone Sarcoma: -Osteo -Ewing	 24 6	 80 20	 28 2	 93.3 6.7	.474	.254
Chemotherapy Name: - -Methotrexate -Adrymicine	 24 6	 80 20	 28 2	 93.3 6.7	.274	.254
Session duration /hrs: -6 -4	 24 6	 80 20	 28 2	 93.3 6.7	.533	.254

Table (2): Total scores of oral assessment guide pre and post oral cryotherapy between study and control groups in percentage distribution (n=60)

OAG Total Scores	Days															
	pre cryotherapy				3rd post cryotherapy				4th post cryotherapy				5th post cryotherapy			
	Study		Control		Study		Control		Study		Control		Study		Control	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Healthy oral cavity (8)	30	100	30	100	28	93.3	0	.0	21	70	0	.0	1	3.3	0	.0
Moderate stomatitis (9-16)	0	.0	0	.0	2	6.7	23	76.7	9	30	22	73.3	29	96.7	14	46.7
Sever stomatitis (17-24)	0	.0	0	.0	0	.0	7	23.3	0	.0	8	26.7	0	.0	16	53.3
Total	30	100	30	100	30	100	30	100	30	100	30	100	30	100	30	100
X^2	.00				64.1				148.7				46.1			
P	.00				.001				.001				.001			

Table (3): Comparison of mean total oral assessment scores pre and post oral cryotherapy between study and control group (n=60)

OAG Days	Mean ±SD		t-test	P
	Study	Control		
pre cryotherapy	8.0 ±.00	8.0 ±.00	.00	1.00
3rd post cryotherapy	8.1 ±.3	13.7 ± 2.6	-11.629	.001
4th post cryotherapy	8.6 ±1.0	14.3.0 ±2.5	-11.569	.001
5th post cryotherapy	10.1±1.1	18.4 ±1.6	-23.833	.001

Table (4): Relation between total scores of oral assessment guide and cryotherapy application days (n=30)

Total scores of OAG	Cryotherapy application days											
	3rd day				4th day				5th day			
	Continuous		Intermittent		Continuous		Intermittent		Continuous		Intermittent	
	No	%	No	%	No	%	No	%	No	%	No	%
Healthy oral cavity(8)	18	60	10	33.3	13	43.3	8	26.7	0	.0	1	3.3
Moderate stomatitis (9-16)	0	.0	2	6.7	5	16.7	4	13.3	18	60	11	36.7
Sever stomatitis (17-24)	0	.0	0	.0	0	.0	0	.0	0	.0	0	.0
X^2	3.214				.106				1.552			
P	.043				.745				.231			

Table (5) Relation between total scores of oral assessment guide at 5th day and child characteristics between study & control group (n=60)

Child Characteristics	Study						Control						X^2	P
	Healthy		Moderate		Sever		Healthy		Moderate		Sever			
	No	%	No	%	No	%	No	%	No	%	No	%		
Age(in years):														
--6-<9	0	.0	1	3.3	0	.0	0	.0	1	3.3	0	.0	.905	.824
-9-<12	0	.0	3	10	0	.0	0	.0	0	.0	3	10		
-12-<15	1	3.3	15	50	0	.0	0	.0	0	.0	8	26.7		
- 15-18	0	.0	0	.0	10	33.3	0	.0	3	10	12	40		
Sex :														
-Male	0	.0	17	56.7	0	.0	0	.0	2	6.7	16	53.3	1.353	.192
-Female	1	3.3	12	40	0	.0	2	6.7	10	33.3	0	.0		
Chemotherapy Name:														
-Methotrexate	18	60	6	20	0	.0	0	.0	21	70	7	23.3	1.429	.232
-Adrymicine	3	10	3	10	0	.0	0	.0	1	3.3	1	3.3		
Session duration /hrs.														
	0	.0	6	20	0	.0	0	.0	0	.0	2	6.7	.330	.566
-6	1	3.3	23	76.7	0	.0	0	.0	4	13.3	24	80		
-4														

6.Discussion

Epidemiologic and genetics studies of childhood cancer showed that malignant bone tumors comprise more than twenty different sub-types, the majority diagnosed as either osteosarcoma (52%) and Ewing's sarcoma (34%) (Stiller, 2010).In the current study, children either diagnosed with osteosarcoma or Ewing's sarcoma. Children followed the NCI chemotherapy treatment protocol which is methotrexate for 6 hours per session or Adriamycin for 4 hours per session respectively.

All children had healthy oral cavity before administration of chemotherapy. Children who received oral ice cubs five minutes before initiation of chemotherapy and half an hour during the chemotherapy session and thirty five minutes after completion of the chemotherapy session had significantly healthier oral cavity than children who did not receive the ice cubs at the third fourth and fifth day post cryotherapy. Similarly, previous researches reported that patients received oral cryotherapy reported less occurrence of mucositis than patients who did not receive it (Worthington, Clarkson & Eden, 2013).Additionally,(Andersoon ,Person & Rahmi,2010) concluded that patients receiving ice chips reported a significant improvement in the daily function activities of swallowing, drinking, eating, etc, compared with patients who did not receive the ice chips.

Mean OAG total score of children who did not receive oral ice cubes was continuously higher than patients who received it. Interestingly, these children score was persistently getting higher from day to day. Worthington and colleagues noted that the mean total scores of children who received ice cubes was significantly less than children who did not (Abu Bakr, etal, 2009).

This study revealed that at 3rd day more than half of children whose sucked ice continuously had healthy oral cavity than who sucked intermittent also minority of them suffered from moderate stomatitis and no one of them had sever stomatitis. There was statistically significant difference, and no significant difference was detected at 4th and 5th day (Keffe etal, 2007) stated that according to previous reports of patients who received cryotherapy following standard dose chemotherapy it has been shown that increasing the time of application did not lead to greater protection and he recommended that optimum duration and intensity of cryotherapy requires further investigation.

There was no significant relation between OAG total scores at 5th day and child age, sex, for both groups. *(Mahmoud etal, 2013)* showed that in study of the female to male ratio for stomatitis was sixty three to fifty two percent, furthermore, grade three and four stomatitis was seen at female to male ratio twenty two to twelve percent, and reported that Stomatitis occurs at least fourty percent of patients undergoing chemotherapy, although other factors such as age, nutrition, type of cancer.

Additionally, there was no significant relation between OAG total scores at 5th day and chemotherapy types and duration for both groups. On the same context (Peterson, 2006) 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 degree of stomatitis.

7.Conclusion

Based on the findings of the current study it is concluded that, cryotherapy was a simple, non-painful ,easily applicable, inexpensive measure , alleviate , decrease the incidence of oral stomatitis and decrease its severity and did not interfere with the efficacy of chemotherapeutic drugs for children with bone tumors. Nursing Implication: In consideration of the valid body of knowledge about oral cryotherapy, it is time for applying them to the practice and oncology nurses are crucial to application of the evidence in those areas. Nurses caring for children treated with chemotherapy should place high priority to prevent oral stomatitis by implication of oral cryotherapy at least for methotrexate and Adriamycin regimens. Finally, our findings support the positive effect of oral cryotherapy on reduction of incidence and severity of this debilitating side effect of single chemotherapy.

8.Recommendations

Based on the main findings of the present study, the following recommendations are suggested:

- Oral cavity should be assessed prior and at least daily following the administration of chemotherapy using standardized oral assessment guide**.**
- Oral cryotherapy must be involved in the routine care for a child who receiving chemotherapy.
- Further study to assess oral cavity 7th and 14th day post chemotherapy.

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