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PREVENTION OF ORAL MUCOSITIS USING CHAMOMILE ORAL CRYOTHERAPY VERSUS ORAL CRYOTHERAPY IN PEDIATRIC CANCER PATIENTS RECEIVING CHEMOTHERAPY: A RANDOMIZED PILOT STUDY

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ABSTRACT

Objective: To assess the prevention of oral mucositis using chamomile oral cryotherapy versus oral cryotherapy in pediatric cancer patients receiving chemotherapy.

Methods: The study included participants aged 6 to 18 years diagnosed with osteosarcoma undergoing chemotherapy (Methotrexate), with intact oral mucosa, and no history of administration of any antiviral or antifungal therapy for oral mucositis. The study population consisted of 20 patients and was divided equally into two groups; (Group A) using the chamomile oral cryotherapy and (Group B) using oral cryotherapy. Oral mucosa was evaluated at baseline, 8th, 15th and 21st day using the Children International Mucositis Evaluation Scale (ChIMES) and the World Health Organization Oral Mucositis Toxicity Scale (WHO mucositis scale).

Results: For the patient reported oral mucositis, the total ChIMES score was higher in patients in group B on all evaluation times with a median and range values of [0(0-1) for baseline, 6(2-12) for day 8, 7.5(4-12) for day 15 and 2(1-6) for day 21]. According to WHO mucositis scale, patients in chamomile oral cryotherapy group never developed grade 2 or higher mucositis with a statistically significant difference found between both groups at day 15 (80% grade 2 in control group versus 0% in chamomile group).

Conclusions: Chamomile oral cryotherapy showed better results in reducing the incidence and severity of chemotherapy-induced oral mucositis in comparison to oral cryotherapy.

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INTRODUCTION

Oral mucositis is a term used to describe the inflammation and ulceration of oral tissues caused by the cytotoxic therapy used for cancer [1]. The inflammation is characterized by edema, pain bleeding and ulceration of the mucosal lining of the oral cavity, pharynx, larynx and the esophageal areas. Previous studies stated the higher incidence of oral mucositis with 40% incidence in patients receiving standard chemotherapeutic treatment for cancer and up to 76% incidence in those undergoing bone marrow transplantation [2, 3].

Prevention of such painful complication is advantageous aiming to improve the nutritional status, hydration and quality of life of the affected patients [4]. Among the various methods for prevention of oral mucositis, oral cryotherapy was recommended due to its ease of application, low cost, pain reduction and bleeding control [5].

Oral cryotherapy has been used in reduction and prevention of oral mucositis by causing vasoconstriction of the blood vessels reducing the local effects of cytotoxic drugs in the cooled area [6]. However, oral mucositis still occurs in approximately 40% of patients receiving cryotherapy, which may be due to inability to prevent the inflammatory process caused by the chemotherapy cytotoxic effect [7].

Recently, natural herbal remedies as chamomile, turmeric and sage were used for prevention of chemotherapy induced oral mucositis due to the popular belief that they are totally safe [8]. The chamomile plant (Matricaria chamomilla) is one of the most widely used herbs in pharmaceutical products worldwide for its anti-inflammatory, anti-bacterial, antifungal, antioxidant and healing ability [8]. It is considered as a noninvasive preventive intervention for oral mucositis as it reduces the inflammatory activity and accelerates the process of mucosal repair [9]. A previous study conducted on hamsters showed a reduction in tissue levels of proinflammatory cytokines indicating the anti-inflammatory action of chamomile over oral mucositis[10]. A previous quasi-experimental study conducted using oral cryotherapy was found effective in reduction of the severity of chemotherapy induced oral mucositis in children with bone tumors [11].

Additionally another clinical study conducted on pediatric cancer patients using chamomile mouthwash revealed a significant decrease in the incidence of chemotherapy induced oral mucositis [12].

Chamomile is recognized as generally safe according to the Food and drug administration (FDA GRAS) lists. Recently, two clinical studies tested the effect of chamomile as a frozen infusion or a mouthwash in adults and showed no toxic effect related to the use of chamomile plant [7] [13]. To our knowledge, safety in young children has not been established, although there was no evidential reports of toxicity caused by the chamomile plant [14].

Therefore, the aim of the study is to assess the effect of chamomile oral cryotherapy on preventing chemotherapy-induced oral mucositis and decreasing its severity in comparison to oral cryotherapy using plain water.

Research Hypothesis

Chamomile oral cryotherapy is not more effective than plain oral cryotherapy in reduction of the intensity and the severity of chemotherapy induced oral mucositis.

SUBJECTS AND METHODS

Approvals and Committees

The study was carried on after being reviewed and approved by the Evidence Based Committee, Faculty of Dentistry, Cairo University, the board of Pediatric Dentistry Department, Faculty of Dentistry, Cairo University and the Research Ethical Committee (REC) (No.: 8-9-18) of the Faculty of Dentistry, Cairo University and the Institutional

Review Board (IRB No.: IRB00004025), National Cancer Institute, Cairo University, Egypt.

Study Design and Sample Size Calculation

This is a randomized single blinded pilot study using parallel group with 1:1 allocation ratio.

The sample size was determined by the Evidence Based Center, Faculty of Dentistry, Cairo University. This study compared two groups; group (A): Chamomile Oral Cryotherapy and group (B): Oral Cryotherapy. The chamomile oral cryotherapy has never been used before in children and adolescences, therefore, a pilot study was recommended. According to previous researches by **(Issac and Michael, 1995),** 10-30 participants was considered satisfactory for a pilot study [15].

Study Settings and Recruitment

Patients were recruited from the inpatient and the outpatient clinics of the Pediatric Oncology Department, National Cancer Institute, Cairo University and the inpatient clinic of the Pediatric Oncology Department, Dar El-Salam Oncology Center, Cairo, Egypt.

Between March 2018 and March 2020, all children and adolescences diagnosed with osteosarcoma bone tumor were invited to participate in the study.

Patients aged 6-18 years of both genders fulfilling the following criteria were included:

- Healthy and intact oral mucosa.
- Diagnosed with (osteosarcoma) for the first time.
- Receiving Methotrexate as part of their chemo-therapeutic regimen.
- Legal representatives of patient must be able to read, understand and provide informed consent to participate in the trial.
- No history of dental discomfort related to cold or hot food or beverage intake.

Patients with the following criteria were excluded:

- Patients undertaking any antiviral or antifungal treatment for oral mucositis before enrollment in the study.
- Patient receiving head and neck radiotherapy or undergoing other chemotherapeutic regimen known to cause high incidence of oral mucositis.
- Patients with known hypersensitivity to pollen grains.
- Patients with known intake of anticoagulants.

Patients were randomly allocated to either group via a computer sequence generated list.

A number of 30 patients were assessed for eligibility, of which only 20 met the inclusion criteria. A sample of 20 participants allocated to group A receiving chamomile oral cryotherapy (Test group, n=10) and group B receiving oral cryotherapy alone (Control group, n=10).

Data collection tools

Three tools were used for data collection.

- **A structured interview questionnaire** developed by the researcher once comprehensive review of relevant literature of oral mucositis and chemotherapy. The questionnaire was filled with personal, medical and dental history. Personal history included patient's name, age, address, and gender. History of the medical condition including current chemotherapeutic regimen, systemic diseases, current medication and history of allergies or hypersensitivity was recorded. Dental history was obtained regarding the past dental history, present dental condition as well as the oral hygiene practices performed by the patient.

Oral hygiene practices included frequencies of teeth brushing, flossing, use of any mouthwashes and the frequency of dental visits.

- **World Health Organization Oral Mucositis Toxicity Scale** adapted from WHO Handbook 1979. It included 5 grades of oral mucositis;

grade 0 showing normal oral mucosa, grade 1 (mild) showing painless oral ulcers, edema or mild soreness, grade 2 (moderate) showing painful erythema, edema, or ulcers but patient is able to eat and swallow solid food, grade 3 (severe) showing painful ulcers with extensive erythema, where patient is no longer able to swallow solid food and grade 4 (life threatening) showing extensive mucositis, where parenteral or enteral support is required [16].

- **Children's' International Mucositis Evaluation Scale (CHIMES) questionnaire** developed by Jacobs et al. (2013) The questionnaire was constructed to assess presence of general pain, oral functional impairment, need for medication and presence of oral ulcerations [17]. It included 7 questions four of which is answered using Facial Pain Scale and the last 3 questions are answered using Yes, No or Can't tell.

The questionnaire included questions regarding (1) Amount of general mouth or throat pain, (2) Effect of mouth or throat pain on swallowing, (3) Effect of mouth or throat pain on eating, (4) Effect of mouth or throat pain on drinking, (5) Receipt of pain medication, (6) Receipt of pain medication for mouth or throat pain, and (7) Presence of ulcers. Questions 1–4 each received a score of 0–5 where 5 is the worst degree of symptoms. Question 5 and 6 received a score of 1 if the child had received pain medications or if the child received pain medications because of mucositis. Otherwise, questions 5 and 6 received a score of 0. Finally, question 7 received a score of 1 if oral ulcers were present and 0 if absent. Any question that was scored as missing or 'I can't tell' was excluded from the total possible score. If all the questions were answered, the maximum score was 23. The ChIMES Total Score was the sum of all scores; 'I can't tell' responses and missing responses both received a score of 0.

Data collection Procedures

Diagnosis

The purpose and the procedures of the study were clearly and simply explained to the legal guardians and a written consent was taken from them after inclusion criteria was met and prior to data collection. Verbal assent was obtained orally from the patient.

Each child was interviewed individually in the out and inpatient Pediatric Oncology Departments before chemotherapy session to fulfill the questionnaire sheet.

Intraoral examination

Examination was carried out on a normal chair using disposable diagnostic set, latex gloves and a portable light source.

Patient dental chart was also recorded in the structured interview questionnaire along with the DMF and def caries indices.

Each participant was clinically examined before the application of both interventions and the score of the WHO Oral Mucositis Scale was recorded. Each participant or guardian was also asked to fill in the ChIMES questionnaire which was translated to Arabic.

Patients who agreed to participate in the study watched a video explaining how to perform oral hygiene.

Clinical Procedure

Patients with osteosarcoma received different sessions of polychemotherapy along with extensive surgery.

Patients included in the study followed the National cancer institute chemotherapy treatment protocol which is methotrexate for 6 hours per session or Adriamycin for 4 hours per session respectively [11]. Application of either interventions

took place once during session of methotrexate only followed by 21 days of rest.

Patients in control group received freshly prepared plain ice cubes (each of $1cm^3$) made of only distilled water, while patients in test group received chamomile ice cubes freshly prepared in special ice trays.

The chamomile ice cubes were prepared using 400ml of distilled water and 10 g of ground chamomile flowers. The chamomile oral cryotherapy have never been used in children, however, according to the world health organization, average child dose of chamomile flower for oral administration is 2 grams three times daily [18].

The ice cubes were kept in the freezer for 24 hours prior to the chemotherapy session in order not to melt.

The patient received a cup of ice cubes which was continuously replenished before being emptied. Patients in both groups were instructed to swish the ice cubes around their oral cavities starting 5 minutes before chemotherapy infusion continuing 30 minutes throughout the session and for additional 35 minutes after completion of intravenous chemotherapy session. This timeframe was chosen according to the plasma half-life of methotrexate drug [11, 19]. Patients were instructed to expectorate and continuously replace the melted ice cubes during the time of interventions application.

For younger patients, ice cubes were crushed to facilitate the swishing of the ice. No problems were encountered by the participants regarding the swishing of ice cubes for 30 minutes continuously.

Application of either interventions was done by an assistant operator (attending nurse) to ensure blinding of the principle investigator (assessor). In this study, blinding of the patient and the legal guardian was not possible due to the distinct colour and taste of the chamomile ice cubes. of both interventions [7].

Follow-up was done by the blinded principle investigator at day 8, 15 and 21st following the chemotherapy session. The reason for choosing the mentioned follow up time points was that oral mucositis usually develops 7 to 14 days following the first chemotherapy session, and the symptoms decline within 2–3 weeks [20].

Outcomes

The **primary outcome** of the study was the patient reported oral mucositis which was measured using the **Children International Mucositis Evaluation Scale**. Inter-rater reliability was examined by allowing both the patient and the guardian to answer the questionnaire.

The questionnaire was translated from English to Arabic. Validity of the Arabic version was done in respect to method of validation adapted from Tsang, Siny et al. 2017 and Paiva et al., 2018. Validation was obtained through the translation of the questionnaire from English into Arabic by two translators who are fluent in English. Following that, the two translations were brought together and the resulting version was back-translated into English by two native English speakers who are fluent in Arabic. Four Pediatric dentists tested the questionnaire regarding the content validity and provided the final version without any modifications [21, 22].

Although the questionnaire was validated, the operator used the English version of the questionnaire to ensure patient have answered all the questions to avoid loss of the data. The questionnaire was used due to its better applicability to children in comparison to other scales as it allows the child to express his/ her level of pain severity and oral functions' discomfort in a friendly and easy way [17].

The **secondary outcome** was the clinical severity and presence of oral mucositis and was evaluated using the **WHO mucositis grades**, where it ranged from 0-5 with the higher grades corresponds to worse mucositis. The scale was used due to its ease

of application on children, simplicity in daily use by clinicians and its ability to detect both the subjective and objective measures of oral mucositis [16].

Statistical analysis

Data was analyzed using IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 24 (SPSS Inc., Chicago, IL).

Comparisons between the two groups for normally distributed numeric variables was done using the Student's t-test, while for non-normally distributed numeric variables was done by Mann Whitney test and Kruskall Wallis test.

Comparisons of different observations (effect of time) for the total score was performed using Friedman test.

Comparisons between categorical variables was performed using the Chi Square test. A p-value ≤0.05 was considered statistically significant. All tests were two tailed.

RESULTS

Patients' characteristics in the chamomile cryotherapy group and the cryotherapy group were comparable regarding the age, gender and the oral hygiene measures with no statistical significant difference between both groups. There was no flossing in all patients participating in the trial (Table 1).

CHIMES QUESIONNAIRE

Intragroup comparison

Regarding the ChIMES questionnaire total scores, both groups showed increased values of the total CHIMES scores, where a median of zero was detected at baseline which increased to 3.5 and 5 at the 8th and the 15th days respectively. The median of the ChIMES total scores then declined to 0.5 at the 21st day. The difference by time was statistically significant (p=0.00) (Table 2).

TABLE (1): Comparison of age, gender distribution, Oral hygiene measures and the caries indices in the study groups (Chi Square test).

	Group A	Group B	P Value
Age	15.4±2.55	13±3.8	0.114
Gender	-Males 7 -Females 3	-Males 3 -Females 7	0.074
Oral hygiene measures (Yes/No):			
-Frequency of dental visits	80%	80%	1
-Brushing	20%	40%	0.40
-Mouthwash use	0%	10%	0.30
Caries indices **-**DMF	0-5	0-4	0.77
- def	0-1	0-2	0.22

Significance level p≤0.05, *significant, ns=non-significant.

TABLE (2): Comparison of ChIMES questionnaire total score at different observations within the same group and between groups [median (range)].

		Baseline	8th day	15th day	21st day	P-Value (within group by time)
Intragroup comparison	**Group A**	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-2)	**0.00***
	Group B	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	**0.00***
Intergroup comparison	**Group A**	0 (0-2)	3.5 (1-8)	5 (2-5)	0.5 (0-1)	
	Group B	0 (0-1)	6 (2-12)	7.5 (4-12)	2 (1-6)	
P-Value (between groups)		0.684 ns	0.75 ns	**0.001***	**0.000***	

Significance level p≤0.05, *significant, ns=non-significant.

Intergroup comparison

Although patients in the control group showed higher ChIMES total scores than those in the test group, a non-statistically significant difference was found at baseline and at day 8 (p=0.68 and p=0.75 respectively). However, a highly statistically significant differences was found between both groups at day 15 and 21 regarding the ChIMES total scores (p=0.001 and p=0.00 respectively).

WORLD HEALTH ORGANIZATION MUCOSITIS SCALE

Intergroup comparison

All children in the study had healthy oral cavity at baseline with no statistically significant differences prior to application of both interventions. On day 8 40% of children in test group had healthy oral mucosa in comparison to 10% in the control group showing a statistically significant difference (p=0.14). Regarding day 15, all children in test group showed healthy mucosa to mild stomatitis (10%) while children in the control group showed 80% moderate oral mucositis. At day 21 all children in the test group had a healthy intact mucosa while 40% of the children in the control group showed mild grade of mucositis. A highly statistically significant difference was found between the test group and the control group at day 15 and 21 (p= 0.00, p=0.025 respectively).

Intragroup comparison

In both groups, oral mucositis was not completely prevented and developed to some point during the study. However, patients in the chamomile cryotherapy group showed less severity of oral mucositis in comparison to those receiving oral cryotherapy alone.

All the patients located in the test group reported none to mild grade of mucositis throughout the follow up times. On the other hand, 20% of the children in control group developed moderate grade of stomatitis at day 15 which increase to 80% at day 21. The intragroup analysis showed that there was an increase in the oral mucositis severity in the both groups over the time intervals from baseline to day 21, with statistical significant differences in each group as demonstrated in (Table 3).

Notably, during the study no patient in both groups developed severe or life- threatening grade 3 or 4 oral mucositis.

Finally, no patient reported any toxicity to chamomile throughout the study timeframe.

TABLE (3): Comparison of WHO mucositis scale at different observations within the same group and between both groups.

		Baseline	8th day	15th day	21st day	P-Value (within group by time)
		No. (%)	No. (%)	No. (%)	No. (%)	
Group A	Score0	10 (100)	4 (40)	0	10 (100)	0.000*
	Score1	0	6 (60)	10 (100)	0	
	Score2	0	0	0	0	
Group B	Score0	10 (100)	1 (10)	0	6 (60)	0.000*
	Score1	0	7 (70)	2 (20)	4 (40)	
	Score2	0	2 (20)	8 (80)	0	
P-Value (between groups)		1 ns	0.144 ns	0.00*	0.025*	

Significance level p≤0.05, *significant, ns=non-significant.

DISCUSSION

Patients with osteosarcoma were selected due to its high incidence and prevalence in childhood (52%) and due to the chemotherapy treatment protocol administrated containing high dose methotrexate (12 g/m^2 over 4 hour infusion). This is of great importance as oral mucositis is mostly caused by high dose chemotherapy regimens [23] [24].

Additionally, two studies stated that patients receiving high doses of chemotherapy or undergoing bone marrow transplantation have a 76% increased incidence of getting mucositis [2] [3].

The current study included patients aged 6 to 18 years old. This age range was decided in relation to the peak incidence of bone tumors in children [25].

Patients were eligible to participate in this study with only intact healthy oral mucosa and absence of any dental problems to allow the proper detection of the mucositis preventing abilities of each intervention and to avoid discomfort by the coldness of the ice cubes due to dental cavitation or exposed roots.

The application time for either cryotherapies was determined to be 5 minutes prior to the chemotherapy session, 30 minutes during the session and 35 minutes after completion of the intravenous chemotherapeutic session. This duration was chosen according to the plasma half-life and the mean concentration of methotrexate, where the mean MTX concentration were maximal after 30 minutes of administration and rapidly decline with an estimated half-life of 30- 60 minutes [11, 19].

Intergroup comparison

The total score of chimes questionnaire for each child was higher in group receiving oral cryotherapy alone than in those receiving chamomile oral cryotherapy. Regarding the results of the total ChIMES score, control group showed higher median and range values with a statistically significant difference between the groups (intergroup) at day 15 and 21st concerning the total ChIMES score. One suggested explanation for this is that chamomile acts as an analgesic and anti-inflammatory agent inhibiting the production of cyclooxygenase-2 enzyme. This in turn inhibits the Prostaglandin E_2 production hence, preventing inflammation [26].

This result is also consistent with the results of Dos Reis et al., 2016 who found out that mouth pain scores was higher in the cryotherapy group in comparison to the chamomile group on day 8, 15 and 22nd [7].

Furthermore, chamomile extract was used to promote reepithelization and collagen formation in oral wound healing in rats, which results in normalization of the oral cavity tissues, hence demonstrating the efficacy of chamomile in reducing the severity of lesions [27].

Additionally, Avallone et al. 2000 investigated the analgesic and the anti-inflammatory effects of chamomile and concluded that this effect was probably due to the presence of apigenin and flavonoids components of the chamomile flower that acts to inhibit the inflammation process [28].

The results of WHO mucositis grading system revealed a non-statistically significant difference between the groups (intergroup) at baseline and day 8. This could be explained due to the absence of oral mucositis prior to initiation of chemotherapy session at baseline and due to the course of oral mucositis, where oral mucositis starts by an erythematous area 7 days following administration of chemotherapy. Dos Reis et al., 2016 showed a consistent finding, where it was mentioned that 20% of the patients receiving chamomile cryotherapy showed a WHO mucositis scale grade higher than grade zero at day 8 while 39% of the patient receiving cryotherapy alone showed a WHO mucositis scale grade higher than grade zero at day 8 [7].

Although oral cryotherapy acts to cause vasoconstriction of the oral blood vessels which reduces the amount of cytotoxic drugs reaching the oral mucosa, control group showed a higher WHO mucositis scores with a statistically significant difference between both groups at day 15 and 21st.

In the chamomile group, none of the participants showed a grade 2 oral mucositis, whereas in group B 80% showed a grade 2 mucositis. One possible explanation is the inability of the cryotherapy alone to prevent the cellular inflammation caused by the cytotoxic chemotherapeutic drug, which resulted in the production of cyclooxygenase-1 and cyclooxygenase-2 enzymes. Additionally, a previous in vitro study identified the role of chamomile plant as an anti-inflammatory agent against the production of cyclooxygenase-2 enzyme [11, 14].

Intragroup comparison

Although the results increased over the follow up times at the chamomile group, it was much lower than that of cryotherapy group. This confirms with the study suggestion that cryotherapy made with chamomile reduces the occurrence and the signs & symptoms of oral mucositis when compared to cryotherapy made only with water.

The results of WHO mucositis grading system revealed a statistical significant difference in each group, where values in both groups increased over the observational times. This is in accordance with Napenas et al., 2007 who mentioned that the course of oral mucositis begins 4 to 7 days following exposure to chemotherapy and progress to reach an ulceration by 10 days then spontaneously resolves two to three weeks following the administration of chemotherapy [29].

In both groups no patient developed a mucositis grade of 3 or 4, which suggests than cryotherapy alone is effective in reducing the severity of oral mucositis. The results of this study were found to be in line with another clinical trial conducted by Rashad et al. 2014 who stated that, none of the patients receiving oral cryotherapy developed severe mucositis in comparison to 53% of patients receiving routine oral care for cancer patients. This could be due to the vasoconstrictive effect of oral cryotherapy on mucosal blood vessels causing decreasing exposure of the oral mucosa to mucotoxic agents [11, 30].

Limitations

The limitation of this study was the small sample size due to the study type (pilot study), however, the study could be considered a base for future larger studies to better detect the effect of the chamomile cryotherapy on chemotherapy induced oral mucositis. Additionally, double blinding of the patients and guardians was not feasible due to the difference in the colour of both interventions.

CONCLUSIONS

From the results of the present study, it can be concluded that the incidence and the intensity of chemotherapy induced oral mucositis were much lower in patients receiving chamomile cryotherapy than in those receiving plain cryotherapy. Additionally, use of the chamomile cryotherapy appeared to be an easier method for reduction of chemotherapy induced oral mucositis. Evaluation of oral mucositis using ChIMES questionnaire showed high compliance due to its ease of use and friendly form.

RECOMMENDATIONS

Further clinical studies with larger sample sizes are needed to confirm the effectiveness of chamomile oral cryotherapy and its use in routine care for children undergoing chemotherapy.

Additionally, studies using different forms of ice as ice popsicles for younger children are recommended.

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