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The Effect of Mucoadhesive Gel Containing Satureja Hortensis Extract 1% on Severity of Chemotherapy-induced Mucositis Pain in Children: A Randomized Clinical Trial

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Abstract

Background: One of the symptoms of mucositis caused by chemotherapy is pain. Mucositis management is initiated by assessment of oral hygiene and management of pain. Many uses have been mentioned for Satureja hortensis in traditional medicine. The study was carried out with the aim of determining the effect of Satureja hortensis extract mucoadhesive gel of 1% on severity of mucositis-induced pain in children under chemotherapy.

Materials and Methods

This randomized parallel double-blind clinical trial was carried out on 60 children who were affected by mucositis following chemotherapy in 2016. The samples were randomly assigned into two groups of intervention and control. The intervention group applied Satureja hortensis extract gel of 1% and the control group applied the placebo gel twice daily for 5 days after the onset of mucositis along with routine treatment. Oral mucosa was evaluated daily. Also, the Oucher pain tools and a demographic checklist were used. The data was analyzed using SPSS version 13.0 software.

Results: The obtained data showed that the two groups had statistical difference in terms of the severity of the pain relief during the time, and pain severity reduced from 3.5±2.1 to 0.0 ± 0.0 in intervention group and 3.1 ± 1.8 to 0.4 ± 1.0 in control group in fifth day ($p < 0.001$).

Conclusion

The study showed that the extract 1% of Satureja hortensis is effective in healing mucositis induced pain and can be used as a new treatment method in relieving reducing mucositis pain.

Key Words: Children, Chemotherapy, Mucositis, Pain, Satureja hortensis.

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1- INTRODUCTION

Cancer is the second leading cause of death in children, and its diagnosis may be difficult due to vague and non-specific symptoms (1). Pain is a common symptom in patients with cancer (2). Mucositis is a painful ulcer of gastrointestinal mucosa (3), that is one of the common complications caused by cancer treatment (3-7). Considering basal cells proliferation, the risk of mucositis incidence is three times more in children than in adults (8).

More than 200 anti-cancer drugs have been approved for clinical application. These drugs prevent the proliferation of tumor cells, inhibit tumor angiogenesis, or enhance immune system's performance (9). Patients with cancer who are under either chemotherapy or chemotherapy and radiotherapy have the painful experience of oral mucositis. Mucosal ulceration and injury in the oral cavity and nasopharynx is in the form of erythema and mucositis-induced pain (10). In some children, the development of mucositis leads to pain, bleeding, and inflammation after an intensive period of chemotherapy (11). The management of mucositis is initiated by oral hygiene assessment, diet changes and pain management (7).

Mucositis-induced pain is one of the most uncomfortable complications of cancer treatment, which often leads to reduced food intake and malnutrition, and sometimes causes delay or discontinuation of treatment (12). The pain of mucositis can influence the patient's quality of life (7, 10). This pain can be moderate or severe, and is relieved by observing oral hygiene and using topical or injectable analgesics (12). The pain of mucositis resulting from chemotherapy in children is a considerable clinical problem that often jeopardizes the child's proper nutrition (13). The pain and decreased oral function in relation to mucositis may persist for a long time after completion of treatment (14). Current supportive interventions in order to reduce the pain and discomfort for patients with oral mucositis consist of improving oral health, soft diet, mucous coating agents, cryotherapy, and systemic analgesics (3). Various standard treatments are used for treating mucositis-induced pain, among which mucous coating agents, topical and systemic anesthesia, and use of topical analgesic narcotics such as Lidocaine and Diphenhydramine can be named. These methods often relieve the pain for 30 minutes, and the contact of these topical materials with oral mucosa causes irritation and change of taste in the mouth (10). Narcotics (opioids) cannot be also used extensively (15).

In refractory cases (resistant to treatment), topical or systemic corticosteroids can be considered; however, secondary candidiasis is a common side effect of topical steroid treatment and in this case, the topical antifungal treatment should be initiated (7). Summer savory with the scientific name of Satureja hortensis is an annual, gramineous semi-woody plant (herb) that is one of higher flowering plants and dicotyledons often spread in Mediterranean areas. The ingredients of Satureja hortensis include materials such as Carvacrol, Thymol, Beta-Pinene, Paracemenu, Lemothen, Camphene, minerals, and vitamins (16). Carvacrol has antimicrobial, analgesic, anti-inflammatory and antioxidant effects (17), so can be considered in prevention of oral inflammations (18-20).

In traditional medicine, this herb has therapeutic uses such as antispasmodic, anti-diarrhea, stimulation of reproduction and treatment of digestive disorders (21-23). Anti-bacterial, anti-inflammatory, anti-fungal and antioxidant properties have been also mentioned for Satureja hortensis (21, 23, 24). Considering the prevalence of mucositis in children under chemotherapy, as well as serious complications of mucositis and the pain caused by it on the treatment process and patients, using the

Satureja hortensis compound that has anti-inflammatory and analgesic properties may play an important role in reducing mucositis-induced pain in these patients. Therefore, this study was carried out with the aim of determining the effect of Satureja hortensis extract 1% on severity of mucositis-induced pain and it's healing in children under chemotherapy.

2- MATERIALS AND METHODS

2-1. Trial design and patients

This randomized parallel double-blind clinical trial was carried out on 60 children with cancer, who had been afflicted by mucositis due to chemotherapy at the Tabriz Children's Hospital from August to November, 2016. Tabriz Children's Hospital is pediatric education center is the refugee center in the North West of Iran. The oncology department of the hospital has 40 active beds covering several provinces. After obtaining the consent, eligible children were included in the study by the method convenience sampling, considering the inclusion and exclusion criteria. Participants using software Rand list considering 60 samples in two groups of 30, permuted block randomization with four and six block sizes in two groups of Satureja hortensis extract 1% gel and placebo with a ratio of 1: 1 allocation were given. To observe blinding of the study, the placebo gel had been prepared and coded by a pharmaceutics group at the Tabriz faculty of pharmacy, exactly like Satureja hortensis extract gel, and the researcher and healthcare provider were not aware of the type of gel. Permuted block randomization was done by the master of the first guide using the software Rand list, the randomization code was 391836736. The gel containing Satureja hortensis extract was applied in the intervention group, whereas the gel without extraction was applied in the control group.

The inclusion criteria consisted of being in the hematology ward or blood clinic; having a history of chemotherapy; full consciousness, being under treatment with Cisplatin, Cyclophosphamide, Methotrexate, Adriamycin and Vincristine, age range of 3-14 years, disease diagnosis such as: Acute Myloid Leukemia, Acut Lymphoblastic Leukemia, Lymphoma, Neuroblastoma, Wilms' tumor, connective tissue sarcoma, brain tumor, and not suffering from recurrent oral infectious damage. Also, the subjects were excluded from the study in cases of the child's and parent's unwillingness to continue the participation in the study, child's death, becoming connected to ventilator, and continuous use of narcotic painkillers for relieving the pain. Each child had same chance of being in the study according to inclusion and exclusion. The process of the study has been shown in **Figure.1**. Hospitalization in the oncology department, patients' clinical records and history of chemotherapy was the criterion for diagnosis of cancer.

2-2. Data collection

A demographic information questionnaire, as well as medical and pharmaceutical history was used to collect clinical and demographic information. The questionnaire was completed for each child through the interview with the child's healthcare provider and according to the child treatment record. Also, the Oucher pain tools as the oldest, most valid and most usable self-report scale of pain severity in children were used to investigate the severity of mucositis-induced pain. This scale consists of 6 photos of a child's face with various severity of the pain that has been rated from 0 to 5, with 0 being a child without the pain and 5 indicating a child with unbearable pain (25).

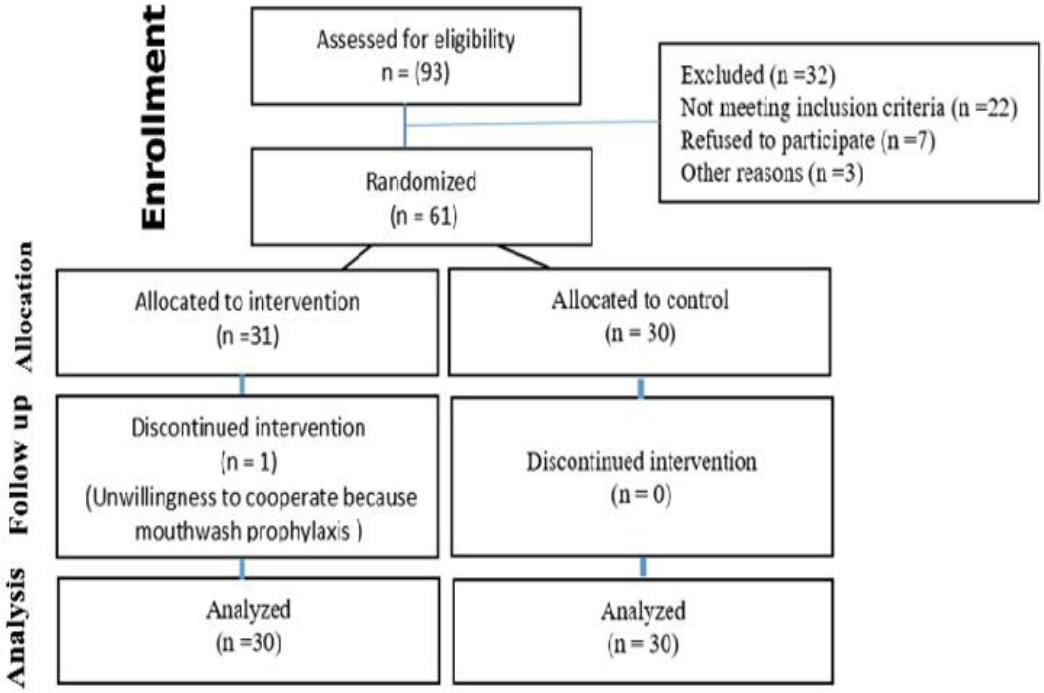

Fig1: Consort diagram showed the flow of participants in the study.

2-3. Extract and mucilage gel

Agricultural Satureja hortensis was used for preparing and extracting the cohesive gel. To do so, the herb was first completely cleaned and washed and then soaked in 70% hydro alcoholic solution and put on the shaker for 72 hours to extract the gel. After this period, the obtained solution was clarified and dried on a rotary operator at the temperature 40°c. This action was repeated on the residues obtained from the first stage. The dried extract was kept closed away from light and humidity until the stage of gel preparation. For preparing the gel, first, the protected water was prepared using methyl and propyl paraben. Then, sodium carboxymethyl cellulose at a concentration of 4% was added to the solution and after stirring of the solution, it could stay at the same state until 24 hours to become fully hydrated. After 24 hours, the appropriate amount of the extract that had been dispersed in water was poured on the first solution and stirred to obtain a gel with concentration of 1%. The whole obtained gel was passed from the three-cylinder mill, filled in tubes of 40gr by a filling machine in aseptic conditions and packed by the machine. The placebo gel was also prepared from the materials used in preparation of Satureja hortensis extract gel, except for Satureja hortensis extract, and was packed in the tubes with the same shape and color. The tubes of mucoadhesive gels were similar in terms of shape, color, consistency, smell, taste, as well as the appearance. Mucoadhesive gel were prepared in closed tubes and coded by the pharmacist, which were mucoadhesive gels delivered to patients, and were used to match smell and taste of lemon oil in both types of mucoadhesive gel. The mucoadhesive gel is used due to its ability in adhering and remaining on mucosal surfaces and slow release of its drug on mucosa due to the permeability and presence of abundant vessels.

2-4. Procedure

In total, 60 children who had conformity with the inclusion and exclusion criteria were included in the study and randomly assigned into two groups of intervention and control. In eligible children who had suffered mucositis because of chemotherapy, first, intraoral examination was performed by cooperation of an oncologist; then, they were included in the study after observing the randomization. To this end, first, the severity of oral ulcer pain was determined and recorded. Then, the mucoadhesive gel was prescribed for each child by the physician. The healthcare provider and child were orally trained about how to apply the gel and after receiving proper feedback, the gel was given to the healthcare provider. The educational pamphlets were also prepared and given to the parents and ward nurses to instruct the method of applying the mucoadhesive gel. For applying the mucoadhesive gel, first, each child washed their mouth with a soft toothbrush; then, put a thin layer of gel with the size of a fin on the healthy mucosa.

Also, the gel was applied after the meal and nothing was eaten until 1 hour after applying the gel. The mucoadhesive gel was applied twice daily, preferably after breakfast and before sleep, and the routine treatment of the ward was also continued along with mucoadhesive gel. Regular consumption of the gel was controlled by the researcher and ward nurses. No child was deprived of the ward's routine treatment that was used for oral ulcer, and the mucoadhesive gel was applied for each child along with the routine treatment. The ward routine treatment consisted of a Cocktail mixture containing 100ml Aluminum Hydroxide-Magnesium Hydroxide-Simethicone syrup (Aluminum Mg.S) (Soha Co. Iran), and 30ml Diphenhydramine syrup (1 ml = 25gr, Sina Daroo Co. Iran), and half of the tube of lidocaine gel 2% (1gr, Sina Daroo Co. Iran), that was being applied for children with mucositis according to the physician's prescription.

2-5. Statistical analysis

The information was collected using SPSS version 13.0 software. The comparison of the qualitative variables was conducted by Chi-square test; while the quantitative variables were compared using t-test and repeated measures ANOVA (The results were significant at ($p \leq 0.05$)

2-6. Ethical issues

To observe ethical issues, an approval with the number IR.TBZMED.REC.1395.282 was obtained from the ethics committee of Tabriz University of Medical Sciences, and the study was registered in Iranian Registry of Clinical Trial site with the number (IRCT- code) IRCT2016061813691N7.

3- RESULTS

Of the 93 children, 22 children were not included in the study due to non-compliance with the inclusion for admission to study, 7 children due to unwillingness of the child or parents and 3 children for other reasons and 61 eligible children were enrolled in the study. One child in the intervention group was excluded from the study due to their parents' unwillingness to continue their collaboration. A total of 60 children who met the criteria for the inclusion criteria included in this study. The mean age was 90.97±41.18 months in the intervention group, and 82.43±37.15 months in the control group, which were statistically equal (P=0.403). The oral ulcer began in 6.0±6.18 and 6.18±8.47 days of hospitalization in the intervention and control group, respectively (P=0.691). The differences were statistically equal and no significant difference was observed between the both groups. Other demographic and clinical information of the patients has been shown in **Table.1**. The analysis of the repeated measures

ANOVA was used in both the groups within 5 days for comparing the severity of mucositis-induced pain, as shown in **Table.2**. As seen in the **Table.2** and **Figure.2**, the severity of oral ulcer- or mucositis-induced pain has been reduced in the both groups during the time; however, the reduction in the mucositis-induced pain severity was statistically different between the both groups and accordingly, the pain was more quickly reduced with more acceleration in the intervention group (P<0.05).

Table 1: The demographic and clinical characteristics of the patients in the two groups of control and intervention

Variables		Intervention group	Control group	P-value
		Number (Percent) n = 30	Number (Percent) n = 30	
Gender	Female	12 (40.0)	8 (26.8)	0.273
	Male	18 (60.0)	22 (73.3)	
Mother's education	Illiterate elementary	11 (36.7)	6 (20.7)	0.139
	Intermediate high school	13 (43.3)	20 (69.0)	
	University education	6 (20.0)	3 (10.3)	
Father's job	Employee	4 (13.8)	5 (16.7)	0.916
	Self-employed	13 (44.8)	11 (36.7)	
	Worker	7 (26.1)	9 (30.0)	
	Other	5 (16.7)	6 (16.7)	
Diagnosis	ALL	12 (40.0)	17 (56.7)	0.409
	Neuroblastoma	4 (13.3)	2 (6.7)	
	Connective tissue sarcoma	7 (23.3)	3 (10.0)	
	Other	2 (6.6)	3 (9.9)	
	Lymphoma	5 (16.7)	5 (16.7)	
Diet	Normal	15 (50.0)	19 (63.3)	0.297
	Low-salt	15 (50.0)	11 (36.7)	
Prophylaxis mouthwash	Yes	4 (13.3)	2 (6.7)	0.389
	No	26 (86.7)	28 (93.3)	
Variables		Mean (SD) n = 30	Mean (SD) n = 30	P-value
Times of hospitalization (month)		14.0 ± 10.8	15.2 ± 9.9	-0.434
Duration of chemotherapy (day)		4.6 ± 2.2	4.0 ± 1.6	1.11
Absolute count of neutrophil *1000		1.5 ± 1.8	2.2 ± 1.6	-1.49
Weight (kg)		25.5 ± 12.6	23.1 ± 10.5	0.814

SD: Standard deviation; ALL: Acute lymphoblastic leukemia.

Table-2: The comparison of the severity of mucositis-induced pain in 5 days between the two groups of intervention and control

Time	Intervention group	Control group	P- value*
	Mean (SD), n = 30	Mean (SD), n =30	
First day	3.5 ± 2.1	3.1 ± 1.8	P<0.001
Second day	1.8 ± 1.4	2.5 ± 2.0	
Third day	0.2 ± 0.5	1.9 ± 1.6	
Fourth day	0.0 ± 0.0	1.1 ± 1.4	
Fifth day	0.0 ± 0.0	0.4 ± 1.0	

*: Repeated measures ANOVA; SD: Standard deviation.

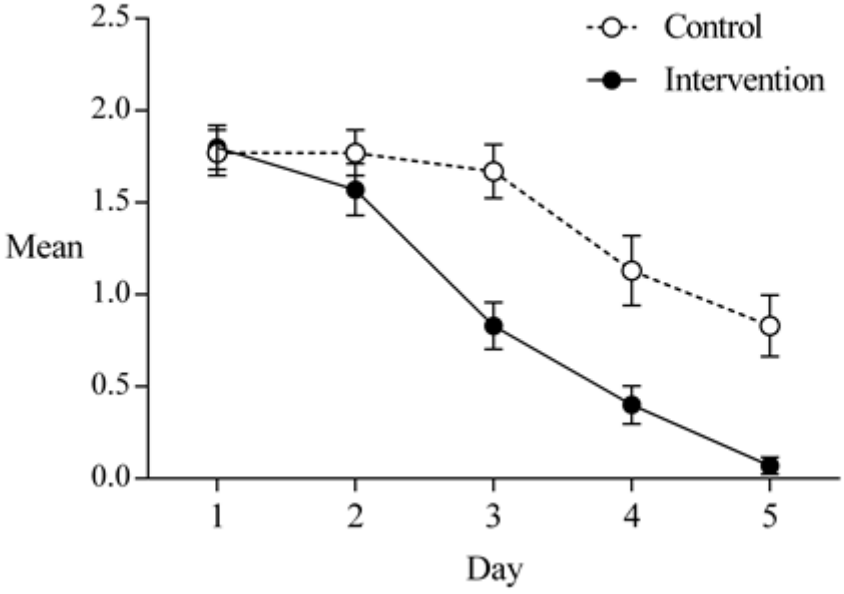

Fig.2: The diagram of the sererity mucositis pain in 5 day between two groups (intervention and control).

4- DISCUSSION

The complications of chemotherapy can have destructive effect on children's life quality, and increase the rate of their mortality. Thus, prevention of intensification of the symptoms caused by drugs and treatment of complications is of nursing care priorities (26). Satureja hortensis is an herb with anti-inflammatory and analgesic properties (21, 24, 27). Therefore, a topical analgesic treatment method in oral mucosa can be an appropriate method for reducing mucositis-induced pain, and an alternative for systemic analgesics and opioids (13). The results obtained from this study showed that mucoadhesive gel containing Satureja hortensis extract of 1% led to the reduced severity of oral mucositis-induced pain in children under chemotherapy, as compared to the routine method. The proper treatment of mucositis-induced pain is a major challenge for healthcare providers. Few studies have been carried out on topical treatments of mucositis pain. The study of Bornemann-Cimenti et al. about topical treatments of mucositis-induced pain was based on experience, and not based on scientific evidence (12). Now, opioids (narcotics) are the most effective treatment for mucositis pain; nevertheless, the tolerance of narcotics and analgesic responses is various in patients, which is attributed to genetic diversity. Although pain is one of the most uncomfortable symptoms for patients, few studies in the field of mucositis have proceeded to direct survey of pain (3). Various studies have been carried out regarding the effect of different topical methods on treatment of mucositis pain. In a study, Shillingburg et al. investigated the effect of ketamine mouthwash on severe mucositis pain in patients under chemotherapy who had suffered grade 3 and 4 mucositis according to the World Health Organization (WHO) criterion, and showed that ketamine had significantly reduced the pain severity and could be an adjuvant treatment in management of severe mucositis (4). Samdariya et al. in a study showed that honey can be effectively

used as a tasty, cheap and accessible product for reducing mucositis-induced pain (28). Guo and colleagues who investigated the effect of fentanyl transdermal on chemotherapy-induced mucositis pain showed that transdermal fentanyl is an effective alternative for other opioids to treat moderate to severe chemotherapy-induced mucositis pain. This drug is safe and well tolerated, and it considerably improves the quality of life (15) . The results of these studies demonstrate mucositis pain relief by using topical methods. Nowadays, an increasing number of people across the world use herbal products for preventive and therapeutic purposes (21). Therapeutic effects of Satureja hortensis have been proven in various studies (18, 19, 29, 30).

Delfan et al. in his study showed that the essence (extract) of Satureja hortensis is effective in relieving Post Herpetic Neuralgia pain and more efficient in terms of onset of effect, stability of effect, acceptance and side effects, compared to other medicines (31). Also, researchers in study on the impact of analgesic activity of Satureja khusistanica extract on several models of the pain in a mouse, stated that it can be possible to use Satureja hortensis extract for treating or managing painful conditions (32), which is compatible with the results mentioned above.

Similarly, this study showed Satureja hortensis extract to be effective in healing the severity of mucositis-induced pain and, in considerably reducing the duration of the treatment of chemotherapy-induced mucositis pain in children. Therefore, Satureja hortensis can be used in reducing (relieving) chemotherapy-induced mucositis pain. Despite the repeated trainings and daily pursuits in this study, there was the possibility of inobservance of some related recommendations by the patients and healthcare providers, which is considered as one of the research limitations.

5- CONCLUSION

Based on the findings obtained from the present study, it seems that Satureja hortensis extract mucoadhesive gel of 1% can be effective in treatment of chemotherapy-induced mucositis pain. Therefore, considering the results of previous researches, which have shown the effect of Satureja hortensis in prevention and treatment of oral damages, as well as the findings of the present study, it seems that applying the extract of this herb is effective in treatment of oral mucositis-induced pain, especially that the preparation of this herb is less costly for the patient compared to the other chemical mouthwashes. Also, considering a long history of herbal medicines use in the world, children and their healthcare providers are more willing to use herbal medicines.

One of limitation of this study is a small number of patients, and it is recommended that a study be conducted with a larger sample size and in several different treatment centers, as well as the individual and physiological characteristics of the patients as another limitation of the study, which was excluded He was a researcher's control. It seems that it is possible to apply the extract of Satureja hortensis for managing chemotherapy-induced mucositis pain in children, which can be investigated in further researches.

6- CONFLICT OF INTEREST: None.

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