The Effectiveness of Vitamin "E" in the Treatment of Oral Mucositis in Children Receiving Chemotherapy

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The aim of this study was to study the effect of vitamin "E" in the treatment of oral mucositis. 80 patients with oral mucositis were randomly distributed into 2 groups: group A, topically applied vitamin "E" and group B, vitamin "E" was given systemically. The 2 groups were evaluated for 5 days. Results showed that in group A grades of oral mucositis improved significantly, while in group B no significant improvement was noticed.

It is concluded that topical application of 100 mg vitamin "E" twice daily is an effective measure for the treatment of chemotherapy-induced oral mucositis.

Key words: *mucositis, vitamin E, oral*

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INTRODUCTION

Cancer is a major health problem. According to the international agency for research on cancer, each year 10.9 million new cases are diagnosed, 6.7 million deaths, and 24.6 million persons alive with cancer around the world.1 Although cancer is considered rare as a childhood disease, its incidence seems to be increasing by 1% average yearly, and cancer is now the main cause of death by disease in children between the ages of one and 14 years.[2]

Pediatric cancer patients are usually suffering from serious oral and dental complications during treatment; these complications might be from the malignant disease itself or to the various modalities of cancer therapy.[3-6]

Both radiation and chemotherapy are important modalities used in the treatment of cancers. They have similar mechanisms of action by interfering cellular growth and differentiation pathways. Dividing cells are more sensitive to the effects of anticancer therapy.[7,8] The lack of specificity of these chemotherapeutic agents in terms of differentiating neoplastic cells from metabolically active normal cells, in addition to the little margin of safety between the therapeutic and stomatotoxic doses of these drugs are the main factors responsible for the oral complications of chemotherapy.[9,10]

Cells of the oral mucosa, the gastrointestinal tract epithelium, and bone marrow divide rapidly and are more sensitive to chemotherapy than slowly dividing cells elsewhere in the body. Their consequence lead to what is known as the early or acute complications.[8, 9,11] Up to 40% of all patients receiving cancer chemotherapy develop ulcerative, hemorrhagic, or infectious oral complications as well as salivary gland and taste dysfunctions.[4,5,7-13]

Chemotherapy has a dual effect on the oral mucosa; direct and indirect. The direct effect is caused by the treatment-induced stomatotoxicity resulting in mucosal atrophy. The indirect effect is through the systemic effects of chemotherapy, such as bone marrow suppression affecting the severity of oral complications.[7,8,11] Salivary gland dysfunction leads to transient xerostomia that is usually accompanied by oral microflora alterations, increase in the acidity of saliva, and hence interference with the normal masticatory process. [9,14,15]

The ulcerative lesions produced by stomatotoxic chemotherapy is known as oral mucositis. The complex biological process of mucositis has been characterized to occur in four phases: an initial inflammatory/vascular phase, an epithelial phase, a pseudomembraneous ulcerative/bacteriological phase and a healing phase.[7,11]

The earliest signs and symptoms of oral mucositis include erythema and edema, a burning sensation, and an increased sensitivity to hot or spicy food. Erythematous areas may develop into elevated white desquamative patches and subsequently into painful ulcers. The latter are not only often secondarily infected, but also impair nutrition and fluid intake, resulting in malnutrition, dehydration, and severe bleeding which further interfere with mucosal regeneration. [11,16]

Vitamin "E", functions as an antioxidant; it reacts with many oxidant molecules and helps protecting cell membranes from lipid peroxidation by trapping the peroxyl radicals.[17,18] Vitamin "E" also acts as a cell membrane stabilizer, which is postulated by some research-

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es to be the primary mechanism preventing tissue damage. This vitamin possibly stabilizes the membrane by increasing the "orderliness of membrane lipid packaging". This effect allows for a tighter packing of the membrane and in turn greater stability to the cell.[17, 18]

Vitamin "E" toxicity has rarely been documented in humans. Doses up to 1600 IU (international unit) have been commonly administered in studies without observable adverse side effects. Toxicity may be difficult to detect because of the wide variation in daily blood vitamin "E" levels.. The body via bile, urine, feces, and the skin excrete excess amount of the vitamin.[19]

Vitamin "E" has been used in several dental studies. Starasoler *et al* [20] used topical application of vitamin "E" oil for the treatment of primary herpetic gingivostomatitis in an adult. Based upon the successful results obtained from this trial, Wadleigh *et al* [21] used the topical application of vitamin "E" for the treatment of chemotherapy-induced oral mucositis in 18 cancer adult patients. The study compared 5 minutes topical application of 400 IU vitamin "E" twice a day and placebo oil consisting of coconut and soybean oil containing less than 1 mg of vitamin "E" applied in a similar manner. The patients were evaluated for 5 days. The study excluded infected lesions, and included head and neck cancer patients. The results of this study were successful, but did not show whether the beneficial effect of vitamin "E" was a result of its local application or because of its systemic absorption.[21] More recent studies found similar successful results.[22,23]

Recently, Ferreira *et al* [24] studied the prophylactic effect of topical vitamin "E" in head and neck cancer patients for the prevention of radiation-induced oral mucositis. Fifty-four adult patients with oral squamous cell carcinoma received either vitamin "E" 400 IU just before radiotherapy and twice daily or placebo 500 mg capsules of primrose oil supplied in the same manner. The study was very successful, vitamin "E" was very well tolerated by the patients, and afforded marked reduction in the incidence of severe radiation induced oral mucositis.

The most recent study conducted by Yörük *et al* [25] studied the prophylactic effects of systemic application of vitamin E and L-carnitine supplementation, separately or in combination, on radiation-induced oral mucositis in a rat model. Vitamin "E" was given intramuscularly in a dose of 40 mg/kg/daily. Vitamin "E" significantly delayed the onset, the severity of the mucositis, and reduced the drop in the numbers of platelets and white blood cells caused by the radiation.

Previous studies have been mainly conducted in adult patients. Vitamin "E" has been shown to be inexpensive, easily available, well tolerated, and a healthy nutrient pediatric patients who are unfortunately at a higher risk for developing oral mucositis.

The aim of this study was to compare the effect of vitamin "E" topically and systemically in the treatment of chemotherapy-induced oral mucositis.

MATERIALS AND METHODS

One hundred and fifty pediatric patients under the age of 12 years undergoing chemotherapy were randomly selected from the Oncology Department, Faculty of Medicine, Alexandria University, and from El-Talaba hospital of Alexandria. All the patients were subjected to an oral examination the dental and medical history and the general health information were recorded. Out of all examined patients only those who exhibited signs of chemotherapy induced oral mucositis (n = 80) were selected to participate in this trial.

All exams were performed at the Pediatric oncology units. Some patients were at the outpatient clinic but most of them were hospitalized. The patients were examined during daylight using latex gloves, plain mouth mirrors and wooden tongue depressors. The patients were examined for: Chemotherapy-induced oral mucositis scoring according to WHO classification:[16]

- Grade 0: No change.
- Grade 1: Soreness/erythema.
- Grade 2: Erythema, and Ulcers; patient can eat solids.
- Grade 3: Ulcers; the patient requires liquid diet only.
- Grade 4: The oral nourishment is not possible.

Patients were randomly assigned into 2 groups: Group A (n = 40) received topically applied vitamin "E" and Group B (n = 40) were given systemic vitamin "E". Instructions were given to the parents of both groups to perform the following palliative treatment[11,15, 26,27]:

• Oral hygiene techniques, which were individualized for each patient according to his/her ability to tolerate soft tissue manipulation. Patients were advised to perform frequent and effective mechanical plaque removal using a soft toothbrush. In cases of pre-existing mucosal irritation or thrombocytopenic hemorrhage, cotton swabs or sponges were used instead.

• Normal saline or mild solutions of sodium bicarbonate (1 tsp per cup of water) were recommended as mouth rinses several times daily.

• Lip lubrication (glycerin, cocoa butter, Vaseline) was also recommended.

• Sugar free chewing gums to enhance oral moistness.

• Certain types of foods were eliminated from the child's diet as the hard foods, nuts, spicy foods, acidic juices, and foods and liquids at extreme temperature.

Group A (topical vitamin "E"):

In addition to the palliative measures, the parents were instructed to empty the oil contained within 100 IU soft gelatinous capsule which is equivalent to 100 mg of vitamin "E"(Pharco Pharmaceuticals, Egypt) without exceeding the maximum daily recommended dose (25 IU / Kg). The capsule was emptied into the child's oral cavity twice daily by piercing it with sterile wrapped needles. Parents were also instructed to wear plastic gloves during these procedures. For older children, the patients were instructed to chew the vitamin "E" capsule and keep the oil in their mouth for few minutes then swallow it.[21,23]

Group B (systemic vitamin "E")

In addition to the palliative measures, the children were instructed to swallow 100 IU soft gelatinous capsule of vitamin "E" twice daily without exceeding the maximum daily recommended dose.

Both groups were followed for 5 days in order to monitor any changes in the oral mucositis scoring level. All data were collected and analyzed statistically using a Wilcoxon signed ranks test with the SPSS computer program.

RESULTS

The effect of vitamin "E" was evaluated. In group B, 2 patients chewed their capsules instead of swallowing them directly, so they were reintroduced into group A, and the final distribution of patients was 42 patients (52.5%) were included in group A, and 38 patients (47.5%) were in group B.

Oral examination of the patients in both groups revealed that:

In Group A the most common affected sites by oral mucositis were the dorsum and sides of the tongue with 30 patients (71.4%) followed by the buccal/labial mucosa which affected 25 patients (59.5%), subsequently, the palate in 18 patients (42.9%), the gingiva in 16 patients (38.1%), the oropharynx in 6 patients (14.3%), and the least affected was the floor of the mouth with only 4 patients (9.5%).

In Group B the most common affected sites were also the dorsum and sides of the tongue with 28 patients (73.7%), followed by the oropharynx affecting 19 patients (50%), the buccal and labial mucosa 14 patients (36.8%), the palate, 11 patients (28.9%), the gingiva, 5 patients (13.2%), and the floor of the mouth was also the least affected with only in 3 patients (7.9%).

During the follow up period the patients' fate was variable. Out of the 42 patients who received topically applied vitamin "E", 3 patients (7.1%) were not available for follow up, 3 patients (7.1%) did not comply with the treatment, and 6 patients (14.3%) died before the end of the 5 days. At the end of the clinical trial only 30 patients (71.4%) completed the follow up period, and recorded for statistics. Out of the 38 patients who received systemically administered vitamin "E", 3 patients (7.9%) were not available to follow up, and 2 patients (5.3%) died before the end of the 5 days, at the end of the clinical trial only 33 patients (86.8%) completed the follow up period, and recorded for statistics.

Table 1 shows the oral mucositis grades before and after treatment in both topical and systemic groups. After the treatment only 30 patients, with a mean age of 5.75 + 3.38, completed the study.Out of these 30 patients, 24 patients (80%) healed completely, 2 patients (6.7%) presented a grade 1, 2 patients (6.7%) a grade 2, one patient (3.3%) had a grade 3, and one patient (3.3%) a grade 4 oral mucositis. The vitamin "E" response in group A revealed a statistical significant difference ($p<0.001$). While in group B after treatment only 33 patients, with a mean age of 9.30 + 2.44, finished the follow up study. Of these patients, no one showed complete healing, 11 patients (33.3%) presented a grade 1followed by 9 patients (27.3%) with a grade, 9 patients (27.3%) a grade 3, and 4 patients (12.1%) had grade 4 oral mucositis. In group B no statistically significant difference ($p=0.317$) was found.

Table (2) shows the number of cases with improved mucositis grade in both groups: In group A (the topical group), 24 cases (80%) healed completely, 4 cases (13.3%) improved, and only 2 cases (6.7%) did not improve. While, in group B (the systemic group), 31 cases (93.3%) did not improve, 2 cases (6.1%) improved, and none healed completely.

Table 1: The number of patients distributed among the different oral mucositis grades before and after treatment in the two groups:

Grade	Group A (n=30)		Group B (n=33)	
	Before: n (%)	After: n (%)	Before: n (%)	After: n (%)
0	-	24 (80)	-	-
1	11 (36.7)	2 (6.7)	11 (33.3)	11 (33.3)
2	1 (3.3)	2 (6.7)	10 (30.3)	9 (27.3)
3	15 (50)	1 (3.3)	10 (30.3)	9 (27.3)
4	3 (10)	1 (3.3)	2 (6.1)	4 (12.1)
Min – max	1-4	0-4	1-4	1-4
Median	3	0	2	2
Wilcoxon Test	4.40		1.00	
p-value	<0.001*		0.32	

* Statistically significant

Table 2: Distribution of the patients according to the improvement status by group:

Improvement	Group A		Group B	
	n	%	n	%
Did not improve	2	6.7	31	93.9
Improved	4	13.3	2	6.1
Healed completely	24	80	---	0
Total	30	100	33	100

DISCUSSION

All patients who were included in this study were receiving standard dose of chemotherapy whether full dose or modified/reduced dose.

There was some difficulty in diagnosing the oral mucositis of the tongue, which is clinically similar to the fungal infection. The oral mucositis was usually accompanied by fever; it emerged two to three days after the beginning of chemotherapy, with burning sensation of the mucosa as an early manifestation. While the fungal infection was not usually accompanied by fever, it appeared after a state of neutropenia, and it was usually accompanied by an unpleasant odor. The diagnosis became more clear if other areas of the oral cavity were affected whether by oral mucositis or by fungal infection. Vitamin "E" was selected for this study to suit the economic state of the Egyptian society; it is cheap and readily available. It has no side effects and can be used safely during all cancer therapy which could extend for years.The vitamin is non toxic, odorless, tasteless, and well tolerated by the patients although the greasy feeling of the oil was annoying to some patients.

Comparing between the topical application of vitamin "E" which gives both topical and systemic effect if swallowed and the systemic administration was based on the recommendation of Wadleigh *et al* [21] who was the first one to study the topical effect of vitamin "E" on oral mucositis; however, they did not know whether the effect was due to the topical application or the systemic absorption of the vitamin when applied topically.

During the trial, the results of 17 patients were not recorded for variable reasons. Six patients were not available for follow up; 4 of them were admitted to the intensive care unit and the other 2 patients were living outside Alexandria and did not show up. Three patients were affected by severe depression and refused all kinds of medications. Another 8 patients suffering from severe oral mucositis died during the clinical trial. Sonis *et al*.[28] also perceived the relationship between severe oral mucositis and death.

All patients who participated in the clinical trial were followed for 5 days. In group A, the topical application had a success rate of 80% (24 cases), 4 patients (13.3%) of the cases improved but did not heal completely; these patients had infected lesions that delayed the healing of oral mucositis. and a failure rate of 6.7% (2 cases).

The 2 failure cases presented pseudomembranes that were traumatized. Normally, these pseudomembranes are partially attached to the oral mucosa and in most cases there is revascularization of these membranes until complete healing is achieved and they become reattached to the underlying mucosa. On the contrary, if these pseudomembranes are peeled or traumatized by anyone (child, mother), there will be deterioration of the lesions. Thus, patient and parents should be instructed not to touch these membranes, and increase the topical

vitamin "E" to 200 IU three times daily without fear of toxicity.[19] Oral hygiene measures should be preserved.

Thirty one patients from group B, (93.9%) did not improve during the 5 days, but got better later on. Healing was slower than the topical group. Two patients (6.1%) only improved, but did not heal completely during the 5 day follow up period.

By comparing the results of both groups, it was found that topical application of 100 mg vitamin "E" twice daily is an effective measure for the treatment of chemotherapy induced oral mucositis. While, the systemic administration of the same dose of vitamin "E" orally was not as effective. The results obtained from the present study concerning the efficiency of the topical application of vitamin "E" in the treatment of oral mucositis were similar to other authors.[21,23,24] Other authors found that the topical application of vitamin "E" is an effective measure in the management of oral mucositis since it accelerates the healing of these oral lesions and prevents their formation by an anti-oxidation process and a membrane stabilization activity.[17,18]

The infected oral mucositis were more resistant to healing than the non-infected lesions that is why Wadleigh *et al* [21] excluded the infected lesions from their study. In these cases vitamin "E" alone was not enough for the treatment of oral mucositis and the antimicrobial therapy must be given in addition to the vitamin.

In contrast, the results of the present study concerning the efficiency of the systemic administration of vitamin "E" disagree with results by Yörük *et al* [25] who studied the prophylactic effect of systemic application of vitamin "E" in rats and found that there was a significant reduction in the incidence of radiotherapy-induced oral mucositis. This variation may be due to the higher parenteral dose of vitamin "E" (40 mg/kg/daily) used by Yörük *et al* [25] while the dose in the present study did not exceed (25 mg/kg/daily).

CONCLUSION

Oral mucositis is successfully treated by the topical application of vitamin "E", compared to its systemic administration.

Vitamin "E" alone is not enough for the treatment of infected lesions; further studies using vitamin "E" in combination with other agents to treat the infected lesions are needed.

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