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EFFICACY OF SELENIUM IN THE PREVENTION OF RADIOTHERAPY INDUCED ORAL MUCOSITIS: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

INTRODUCTION: Radiation-induced oral mucositis (RIOM) is one of the most common complications in head and neck cancer (HNC) patients and is thought to occur through oxidative stress. Selenium(Se) has attracted tremendous interest because of its importance as an antioxidant and anti-inflammatory agent.

OBJECTIVES: Evaluating the effectiveness of Se in the prevention of radiation-induced oral mucositis(OM).

PATIENTS AND METHODS: A randomized controlled clinical study was conducted on forty head and neck cancer patients undergoing radiotherapy at the Department of Clinical Oncology, Faculty of medicine, Alexandria University, Egypt. Patients were assigned , equally, to either control group who received conventional preventive medications or test group who received 200 mg of selenium twice daily along with the conventional preventive medications. All patients were clinically evaluated for OM severity (objective assessment) and pain (subjective assessment) at day 1 of radiotherapy, day 14, day21 and day 42.

RESULTS: There was no significant difference comparing control and test groups regarding severity of OM and mean pain score during the four times of assessment.

CONCLUSION: The administration of Se supplementation during radiotherapy has no effect on OM severity and its related pain when assessed by World Health Organization (WHO) scale and visual analogue scale(VAS) ,respectively.

KEYWORDS: Antioxidants, Cancer, Radiotherapy, Selenium, Oral mucositis.

RUNNING TITTLE: Effect of selenium in the prevention of oral mucositis.

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INTRODUCTION

Cancer starts by changes (mutations) to the DNA within cells, by instructing a healthy cell to make mistakes while repairing DNA errors, allowing its rapid growth . This creates many new cells that all have that same mutation, if the spread is not controlled, it can result in death (1).

The annual incidence of head and neck cancers worldwide is more than 650,000 cases with around 330,000 deaths each year (2).

Chemotherapy and radiotherapy are preferred treatment modalities for cancer. Although both treatments have good cure rates during the early stages, these treatments can lead to functional impairments (3).

Radiotherapy has irreversible side effects on the oral mucosa such as OM, xerostomia along with added risk of osteoradionecrosis (4,5).

OM has impacts on the quality of life, morbidity and mortality (6).

Selenium, is an essential trace element .It is considered a potent antioxidant , it forms an essential component of important antioxidant enzymes (selenoenzymes) such as glutathione peroxidase (GPx) family , which is involved in regulating oxidative processes and cell membrane protection (7), and is thought to be a major defense in low-level oxidative stress . These selenoenzymes catalyze the reduction of hydroperoxides and lipid peroxides to their corresponding alcohols and water with reduced glutathione (GSH) as the electron donor(8) .It also plays an important role as an anti-inflammatory agent by tightly regulating the expression of pro-inflammatory genes in immune cells and improves the function of immune-component cells (9).

Selenium substitution has been shown to improve phagocytosis, natural killer cell (NK) activity, expression of IL-2 receptors and T cell proliferation as well as immunoglobulin synthesis (10,11).

Regarding OM, some studies have shown that antioxidants can reduce OM severity (12). Ameri et al (2016) suggested that Se may be beneficial in preventing radiation-induced oral mucositis RIOM (13).

Therefore, the objective of this study was to investigate the effectiveness of Se in the prevention of radiation-induced OM . The null hypothesis is that Se has no effect in the prevention of RIOM.

PATIENTS AND METHODS

1-Participants and Study design:

This randomized parallel controlled clinical trial was conducted on forty head and neck cancer (HNC) patients who were going to receive radiotherapy. Patients were recruited from the outpatient clinic of the Department of Clinical Oncology, Faculty of Medicine, Alexandria University, during the period between March 2018 and February 2019. The study was approved by the Research

Ethics committee of the Faculty of Dentistry, Alexandria University, Egypt (IRB NO: 00010556-IORG0008839). A written consent was obtained from all patients after clearly explaining the details of the study.

The control group comprised twenty patients who were given conventional preventive medications (13) from day 1 of radiotherapy to six weeks after, that included: 20 drops of nystatin every three hours, a chewable tablet of sucralfate 500 mg every eight hours and mouth washes containing 10cc chlorhexidine 0.02% plus 10cc diluted povidone iodine every three hours. The test group included twenty patients who were given selenium tablets (200 mg) twice daily from day one of radiotherapy to six weeks after, beside the conventional preventive medications.

2- Sample size

A sample size of twenty patients per group (number of groups = 2) (total sample size = 40 patients) was the enough required sample to detect a standardized effect size of 0.925 change in the primary outcome (14,15), as statistically significant with 80% power and at a significance level of 95% (accepted a of 0.05).

The sample size was calculated using G Power version 3.1.9.2 (16).

3-Criteria for patient selection

The following inclusion criteria were applied: both sexes were included, patients between 30 and 55 years old who were going to receive radiotherapy. None of these patients had received chemotherapy concomitant to radiotherapy four weeks before the study. All patients were taking approximately 2 Gy daily dose of radiation, five days per week, for six continuous weeks or more (17) . Patients who were smokers, alcohol consumers, pregnant and lactating women were excluded. Patients who were suffering from any other systemic diseases or eating spicy and hard food were also excluded.

Randomization in four blocks of ten patients was used to ensure a balanced allocation of eligible patients in the control and test arms. The random allocation sequence was generated using a computer-generated randomized list to achieve allocation concealment. Randomization was performed by an examiner who was not involved in the study. All patients in this study were masked to the type of treatment. All subjects were analyzed in an intention-to-treat manner.

4-Clinical evaluation

Before radiotherapy, detailed medical and dental history were obtained and all patients were subjected to thorough intraoral examination to check for and remove any septic foci. All patients were clinically evaluated four times: day 1 (base line), day 14, day 21 and day 42, using the two following measurements:

OM severity (objective assessment) using the WHO grading system. Based on clinical features of every patient (ability to drink and eat) as well as the presence of lesions (ulcers, erythema). The measurements were categorized to Grade I: asymptomatic or mild erythema and soreness, Grade II: moderate erythema and ulcerations (solid food tolerated), Grade III: confluent ulceration (liquid diet only tolerated) and Grade IV: oral alimentation impossible (18,19).

Discomfort and pain severity were recorded using the VAS (subjective assessment) (20). Using a ruler, the score was determined by measuring the distance (mm) on the 100-mm line between the “no pain” anchor and the patient's mark, providing a range of scores from 0–100 mm as no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75– 100 mm) Patients were asked to assign a numerical score on the scale verbally to rate their pain intensity, and the number was recorded (21).

5-Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and IQR. Significance of the obtained results was judged at the 5% level.

The used tests were:

1 - Chi-square test

For categorical variables, to compare between different groups.

2 - Fisher’s Exact or Monte Carlo correction

Correction for chi-square when more than 20% of the cells have expected count less than 5.

3 - Student t-test

For normally distributed quantitative variables, to compare between two studied groups.

4 - Mann Whitney U test

For abnormally distributed quantitative variables, to compare between two studied groups.

5 - Friedman test

For abnormally distributed quantitative variables, to compare between more than two periods or stages and Post Hoc Test (Dunn's) for pair wise comparisons.

RESULTS

A total of forty out of fifty two patients participated in the present study, three discontinued and nine patients were dismissed. All patients were clinically evaluated at day 1of radiotherapy, day 14, day 21 and day 42 for OM, and pain severity.

Data were collected, tabulated and analyzed as in the following tables:

Table 1 (sex & age)

Table 1 shows the age and the sex of the two groups, age in the group I (control group) ranged from 33 to 55 years with a mean of 45.45 ±6.75, while in group II (test group) age was ranged from 38 to 55 years with a mean of 47.10 ±5.74. No significant difference was found between the two groups (P=0.410).

Sex

In group I , 65% were males and 35 % were females, while in group II , 60% were males and 40% were females. No significant difference was found between the two groups (p=0.744).

Clinical results

1-Regarding OM severity

Table 2, figure 1 show the comparison between the two studied groups according to objective assessment by the WHO on day 1, day 14, day 21 and day 42. Day 1 , both groups showed grade 0 OM (P=0). On day 14 regarding control group 17 patients showed grade 0 OM while, 3 patients showed grade I OM and in the test group 15 patients showed grade 0 OM and 5 patients showed grade 1 OMP=0.695). On day 21, in the control group, 3 patients

showed grade 0 OM, 10 patients showed grade 1 OM and 7 patients showed grade II OM. In test group, 4 patients showed grade 0 OM, 12 patients showed grade I OM and 4 patients showed grade II OM (P=0.683). On day 42, in the control group 6 patients showed grade I OM, 10 patients showed grade II OM and 4 patients showed grade III OM. In test group 1 patient showed grade 0 OM , 5 patients showed grade I OM, 11 patients showed grade II OM and 3 patients showed grade III OM (P=1.000).

Regarding the P values of OM severity there was no significant difference between the two groups.

Figures (3, 4) show dry ulcerated borders of the mouth, mucosal erythema, ulcers and atrophic and coated tongue at day 42 for patients from the two groups.

2-Regarding VAS

Table 3, figure 2 show comparison between the two groups using VAS.

On day1 in both control and test groups, VAS was 0.0 ± 0.0 and (P= 1.000).

On day 14 the control group exhibited a mean of 0.35± 0.88 while in test group, it was 0.55±1.23. (P=0.640).

On day 21 the control group had a mean VAS of 3.15±2.60 while in test group it was 3.10±2.29 (P=0.968).

On day 42 the control group had a mean VAS of 5.80±3.07 while in test group, it was 6.20± 3.0.(P=0.698)

Regarding the P value of VAS score, there was no significant difference between the two groups.

Table (1): Comparison between the two studied groups according to demographic data.

	Control Group (n = 20)		Test Group (n = 20)		Test of Sig.	P
	No.	%	No.	%		
Sex Male Female	 13 7	 65 35	 12 8	 60 40	χ^2= 0.107	0.744
Age (years) Min. – Max. Mean SD.	33.0 – 55.0 45.45 6.75		38.0 – 55.0 47.10 5.74		t= 0.833	0.410

χ^2: Chi square test t: Student t-test
p: p value for comparing between the studied groups
Statistically significant at *p* value ≤ .05

Table (2): Comparison between the two groups according to severity of oral mucositis.

OBJ ASS OF WHO	Control Group (n = 20)		Test Group (n = 20)		χ^2	P
	No.	%	No.	%		
Day 1 0 I II III	 20 0 0 0	 100.0 0.0 0.0 0.0	 20 0 0 0	 100.0 0.0 0.0 0.0	–	–
Day 14 0 I II III	 17 3 0 0	 85.0 15.0 0.0 0.0	 15 5 0 0	 75.0 25.0 0.0 0.0	0.625	FEp= 0.695
Day 21 0 I II III	 3 10 7 0	 15.0 50.0 35.0 0.0	 4 12 4 0	 20.0 60.0 20.0 0.0	1.182	MCp= 0.683
Day 42 0 I II III	 0 6 10 4	 0.0 30.0 50.0 20.0	 1 5 11 3	 5.0 25.0 55.0 15.0	1.316	MCp= 1.000

χ^2: Chi square test MC: Monte Carlo
FE: Fisher Exact
p: p value for comparing between the studied groups
Statistically significant at *p* value ≤ .05.

Table (3): Comparison between the two groups according to the visual analogue scale (VAS).

VAS	Control (n = 20)	Test (n = 20)	U	P
Day 1 Min. – Max. Mean ± SD. Median (IQR)	 0.0 – 0.0 0.0 ± 0.0 0.0	 0.0 – 0.0 0.0 ± 0.0 0.0	200.0	1.000
Day 14 Min. – Max. Mean ± SD. Median (IQR)	 0.0 – 3.0 0.35± 0.88 0.0 (0.0 – 0.0)	 0.0 – 5.0 0.55±1.23 0.0 (0.0 – 0.50)	182.50	0.640
Day 21 Min. – Max. Mean ± SD. Median (IQR)	 0.0 – 8.0 3.15±2.60 2.50 (1.0 – 5.50)	 0.0 – 8.0 3.10±2.29 3.0 (1.50– 5.0)	198.0	0.968
Day 42 Min. – Max. Mean ± SD. Median (IQR)	 1.0 – 10.0 5.80±3.07 6.50 (3.0 – 8.0)	 0.0 – 10.0 6.20± 3.0 7.0 (3.0 – 8.50)	185.50	0.698

U: Mann Whitney test
p: p value for comparing between the studied groups
Statistically significant at *p* value ≤ .05

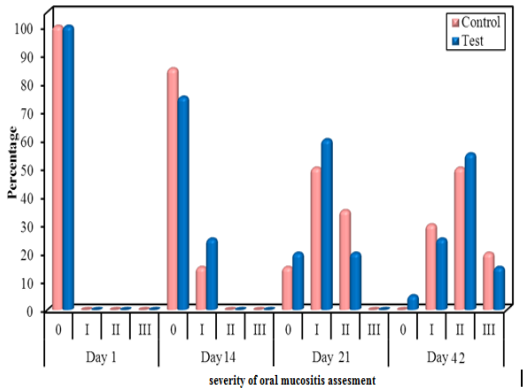

Figure (1): Comparison between the two groups according to severity of oral mucositis.

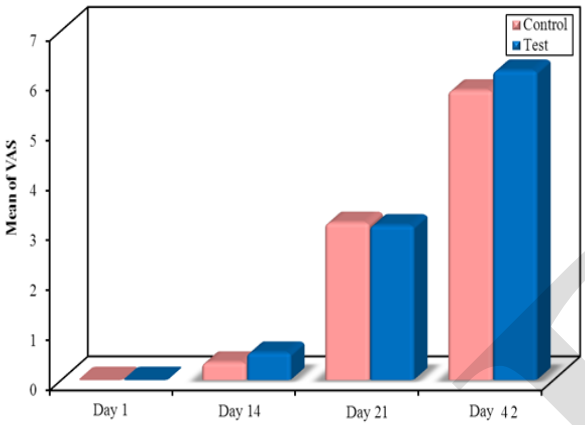

Figure (2): Comparison between the two groups according to VAS

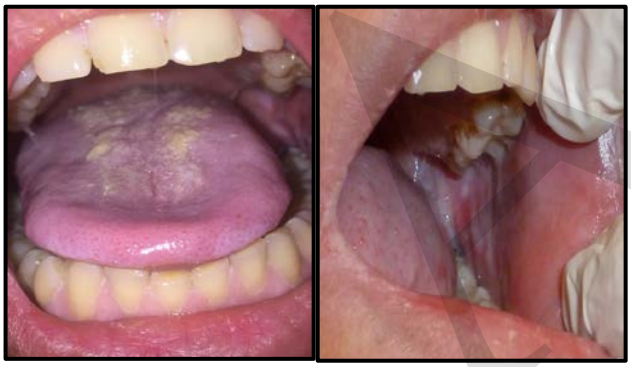

Figure (3): OM. at day 42 for a control group patient.

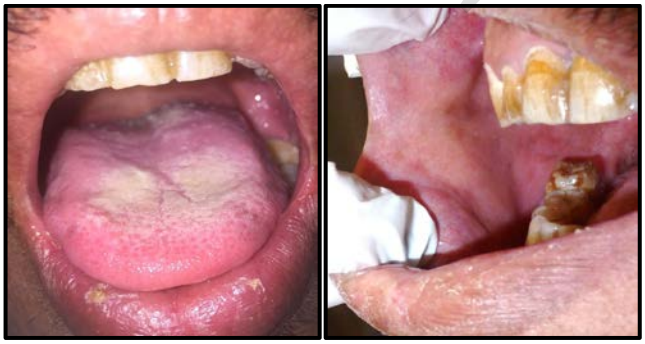

Figure (4) : O.M. at day 42 for a test group patient.

DISCUSSION

The mucosal lining of the gastrointestinal tract, including the oral mucosa, is a prime target for treatment-related toxicity by virtue of its rapid rate of cell turnover. The oral cavity is highly susceptible to direct and indirect toxic effects of cancer chemotherapy and ionizing radiation (22).

Oncologists frequently encounter OM, which can be severe and cause hospitalization or unplanned breaks in radiotherapy (23).

Antioxidant supplementations during conventional chemotherapy and radiation therapy could be beneficial (24). Within the group of antioxidant minerals, Se has a special importance amongst others because it is a cofactor of antioxidant enzymes such as glutathione peroxidase and thioredoxin reductase(25).

The study sample was selected from patients having HNC receiving radiotherapy with an age range between 30 and 55 years. Both groups had the same age range as younger patients tend to develop OM more often than older patients. This appears to be due to the more rapid rate of basal cell turnover noted in younger patients (26). However, the healing of OM is also more rapid in the younger age group. Smokers were excluded as smoking impairs wound healing (27) Similarly , patients with alcohol intake or patients who eat spicy and hard food were excluded as they these factors are known to aggravate mucositis and increase pain level (28).

Pregnant and lactating patients were also excluded as Se crosses the placenta (29) and the nystatin used in the study is FDA pregnancy category C .Similarly, it is not known whether nystatin and sucralfate can pass into breast milk and harm the nursing baby (30).

Patients with other systemic diseases were excluded as they require more consultations and other considerations that could affect the results.

Patients taking chemotherapy during radiotherapy sessions or four weeks prior were also excluded in order to eliminate all possible causes that might induce OM, as chemotherapy induced OM usually persists up to 4 weeks (31).

Maintaining good oral hygiene and adequate hydration were mandatory for both groups to avoid any exacerbating factor for oral lesions (32, 33).

Patients fulfilling the inclusion criteria were randomly distributed among two groups, control and test. Randomization was done to ensure that all factors influencing the study outcome were equal.

A total of forty out of fifty two patients participated in the present study, three patients discontinued and nine patients were dismissed from both groups because they experienced severe OM and their radiation sessions were interrupted by their oncologists to give them time to heal, then resume their sessions again. This could be the reason why severe OM was not recorded in the present study (no cases with grade 4 OM was recorded in both groups) (34).
Patients were evaluated clinically through objective and subjective assessments using WHO scale and VAS, respectively.

Discomfort and pain severity were recorded for each patient on day 1 of radiotherapy, day 14, day 21 and day 42.

For objective assessment regarding OM severity using the WHO scale and subjective assessment using VAS scale between the two groups during the assessment periods, on day 1 of radiotherapy, day 14, day 21 and day 42, there was no statistically significant difference between the two groups.

This study concluded that Se has no effect on preventing OM, which is in line with a similar study by Eroglu et al in 2012 who suggested that serum selenium levels do not affect radiotherapy related toxicities (35).

On the other hand, this is in contrast with a report by Ameri et al which concluded that oral selenium can be considered as an effective and well-tolerated medication for the prevention of radiation induced OM (13).

An interesting point to be considered is that the present study discussed the effect of selenium in preventing only radiation induced OM, by its administration from day 1 of radiotherapy and every day throughout 42 days. A point arises here as to whether the same effect will still hold true if Se were administrated a few days or a week prior to radiotherapy .

The limitations of this study were that we could not prevent xerostomia and maintain adequate hydration once OM developed, patients could not tolerate drinking large amounts of water to maintain hydration and prevent xerostomia (36-38), also a larger sample size was needed , in addition, serum Se level was not considered from the beginning for all patients to correlate between RIOM and Se status and to prevent Se toxicity.

The strength of this study was based on excluding the effect of chemotherapy as we evaluated only radiotherapy induced OM during the six week study period.

CONCLUSION

The administration of Se with conventional preventive medications has no effect on preventing or alleviating the severity of OM, and its related pain in comparison with conventional preventive medications alone in patients with RIOM.

Conflicts of interest

The authors declare that they have no conflict of interest.

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