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The protective role of l-Carintine and vitamin E on gamma irradiated rat's tongue mucosa

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► ***Original article***

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ABSTRACT

Background: The aim of this study was to investigate the antioxidant effect of L-carnitine (LC) against gamma-irradiation-induced oxidative damage in tongue of albino rats after total body irradiation with a single dose of 6 Gy. ***Materials and Methods:*** 48 adult rats were randomly divided into 3 groups of 16 animals each. Group I was irradiated with a single dose of 6 Gy. Group II received a daily i.p. injection of LC (250 mg/kg, i.p.) for 5 consecutive days and 1 h after the last dose, rats were irradiated with a single dose (6 Gy). Group III received a daily i.p. injection of LC (250 mg/kg, i.p.) and Vitamin E 40 mg/kg intramuscular daily for 5 consecutive days and 1 h after the last dose, rats were irradiated with a single dose (6 Gy). At day 7 and day 14 after treatment exposure, 8 rats from each group were sacrificed. ***Results:*** Administration of LC resulted in attenuation of the histological changes noticed in irradiated rats. The number of p53 positive nuclei significantly decreased in rats receiving LC alone or in combination with VE. ***Conclusion:*** LC and VE has shown positive effect in minimizing the epithelial atrophy of tongue mucosa after radiotherapy, which was emphasized by decreasing apoptotic activity in these tissues.

Keywords: *Gamma irradiation, tongue mucosa, L-carintine, vitamin E.*

INTRODUCTION

Mostly one hundred percent of those experiencing high dose radiation therapy for head and neck cancers suffer from some degree of oral mucositis (OM) [1]. OM was first termed in 1980 as a side effect of radiotherapy (RT) in cancer patients [2]. OM is a normal tissue injury caused by radiation/ RT [3], which starts as an acute inflammation of oral mucosa, tongue, and pharynx after 24 RT exposure and lasts between 7 and 98 days [3, 4].

Cancer therapy directly damages DNA and causes strand breaks that result in the death of a small fraction of basal and suprabasal epithelial cells [5, 6]. A more pronounced effect is believed to be derived from the generated reactive oxygen species (ROS); since they are also important mediators of downstream events that drive tissue damage [7, 8]; or through enzymatic or transcription factor activation in multiple cellular elements within the mucosa [9]. This complex mechanism ends by diminished regenerative capacity of the oral and alimentary epithelium, leading to atrophy, erythema, ulceration, and, usually, the loss of mucosal barrier [10]. This leads to cancer treatment interruption, alterations in radiation dose fractionation and limitations of local tumor control [11-15].

L-carnitine (LC) is a natural compound known as vitamin BT (γ-trimethyl amino butyrate) widely distributed in the body [16, 17]. LC is obtained mostly from the diet, good sources being dairy products, red meat, nuts, and seeds, pulses and fruits such as apricots, bananas and avocado [18] or can be given exogenously. It can also be synthesized endogenously by skeletal muscle, heart, liver, kidney and brain from the essential amino acids lysine and methionine [16,

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19). LC and its derivatives prevent the formation of ROS, scavenge free radicals and protect cells from peroxidative stress (20-26). It therefore plays a modulatory role against the cellular damage produced by free radicals induced by ionizing radiation (27). LC is the only known substance that allows fatty acids to cross the mitochondria membrane, The human body needs an adequate supply of iron, vitamin C, pyridoxine, and niacin for its endogenous synthesis, which takes place mainly in the cytosol and in the mitochondrial matrix of liver and kidney cells. LC is critical for energy generation by mitochondrial ß-oxidation (28); therefore deficiencies must be avoided. It has no known harmful side effects, it possesses extensive anti-oxidant properties and can be used as a supplement against oxidative stress (18).

The radioprotective effect of LC on several tissues including kidney, lens, retina, brain, cochlea, salivary glands, ovaries, small intestine and colon has been shown in earlier studies (29-37).

LC has a capacity to enhance non-enzymatic antioxidants, such as VE (22). Antioxidative micronutrients such as vitamin C, vitamin E, retinoids, and selenium do not act merely as radical scavengers but have many essential metabolic functions in addition to the antioxidant cell protection. They have immunomodulating and apoptosis-inducing properties, as well as regulatory effects on cell proliferation and differentiation (38, 39).

VE physically stabilizes membrane permeability and its fluidity. VE is a potent anti-inflammatory agent (40) and it may not only protect intact tissues by decreasing apoptosis induced by damaging condition (41), but it may also increase apoptosis with a direct selective action on cancer cells (42).

Consequently, recent evidences have demonstrated the antioxidant, anti-inflammatory, and cytoprotective roles of both VE (40, 43, 44) and LC (33, 45-49).

The present study was established to assess the preventive capacity of L-carnitine (LC), alone and in combination with vitamin E (VE), for reducing radiation induced oral mucositis, in terms of preserving the epithelium integrity and decreasing the apoptotic activity.

MATERIAL AND METHODS

Animals

Forty-eight male Albino rats (weighing 120–150g) were obtained from the animal farm of the Egyptian Holding Company for Biological Products and Vaccines, Egypt. Upon arrival, the animals were allowed to acclimatize for 1 week before starting the experiment. Animals were kept under standard conditions and were allowed free access to a standard requirement diet and water ad. Libitum. Animals were kept under a controlled lighting condition (light: dark, 1 1h-11h). The animals' treatment protocol was approved by the animal care committee of the National Center for Radiation Research and Technology (NCRRT), Cairo, Egypt.

Irradiation

Whole-body gamma-irradiation was performed at the National Centre for Radiation Research and Technology (NCRRT), Atomic Energy Authority, Cairo, Egypt, using (137cesium) Gamma Cell-40 biological irradiator. Animals were irradiated at an acute single dose level of 6 Gy delivered at a dose rate of 0.012 Gy/s (50-54).

Horse Radish peroxidase

Collection and preparation

At day 7 and day 14 after treatment exposure, 8 rats from each group were sacrificed by decapitation. Tongue was dissected and immediately fixed in 10 % formalin and embedded in paraffin. Five microns thick paraffin sections were stained by haematoxylin and eosin, for histological evaluation.

For p53 immunostaining, formalin-fixed paraffin embedded tissue specimens were cut into approximately 4-µm thick sections and attached to positively charged glass slides. Before immunostaining, the sections were treated in a pressure cooker reaching maximum temperature of 121°C using Tris-HCL buffered saline, pH 9.0 as retrieval solution. The sections were incubated with a primary monoclonal antibody (anti-p53, clone DO-7, Dako, Glostrup, Denmark) at room temperature for 30 minutes (dilution 1:100). Horse Radish Peroxidase -

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detection system was used (EnVision Plus-HRP, Dako, Glostrup, Denmark) according to manufacturer's instructions. Diaminobenzidine was used as chromogen.

Evaluation of immunoexpression and statistical analysis

The Computer image analyzer system, Leica Qwin 500 software (Leica Microsystems, Wetzlar GmbH, DM LB2/11888111, Germany) was used in counting the number of p53 positive nuclei of in each field. Three fields from each slide were chosen in a standard measuring frame using a magnification of × 400 by light microscopy transferred to the monitor's screen. The number of the positive cells was described as mean values ± standard deviation (±SD). One way analysis of variance (ANOVA) test was used to compare between the studied groups. It was followed by Tukey Post Hoc multiple 2-group comparisons

RESULTS

In group I, seven days following irradiation, crowded nuclei and disrupted architecture of basal cells were noted. Keratin tips were lost over some papillae. In the underlying lamina propria, some blood vessels were dilated; areas of edema and mild chronic inflammatory cell infiltrate could also be noticed (figure 1a). Fourteen days following irradiation, altered basal cell architecture was still noticed but was less obvious in comparison to the previous group. In the underlying lamina propria, smaller areas of degeneration and edema among the collagen fibers were observed (figure 1d).

In group II, seven days following irradiation, the dorsal surface of the tongue presented nearly normal keratinized stratified squamous epithelium without obvious changes in its structure except for localized areas showing reduced keratin height over some lingual papillae (figure 1b). Fourteen days following irradiation, normal tongue mucosa was covered by keratinized stratified squamous epithelium. Normal filliform papillae could be detected. The underlying connective tissue stroma was composed of collagen fibers, fibroblasts and few blood vessels. (figure 1e)

In group III, seven days following irradiation, the dorsal surface of the tongue revealed no significant change. Keratin and lingual papillary height and the basal cell layer architecture were apparently preserved in most areas. (figure 1c). Fourteen days following irradiation, filliform papilla appeared intact, with normal keratiniztion. Sporadic inflammatory cells and some dilated blood vessels were seen in the connective tissue. (figure 1f)

p53 immunohistochemistry

p53 immunostaining was mainly confined to the basal and supra basal layers of the epithelium. Staining intensity was greatest in group I at 7 and 14 days (figure 2 a,d). The number of p53 positive nuclei decreased in group II at both observations times (figure 2 b,e), as well as in group at 7 days, to reach its lowest level at 14 days(figure 2 c,f). ANOVA test revealed a significant difference between groups (table 1, figure 3).

Table 1. Number of P53 positive nuclei in different groups (ANOVA test).

	Group I (Single dose, 6 Gy)		Group II (ALC+ Single dose, 6 Gy)	Group III (ALC+ Vit. E+ Single dose, 6 Gy)		
	7 days	14 days	7 days	14 days	7 days	14 days
Mean	34.67[a]	30.00[a]	17.33[b]	15.46[b]	16.84[b]	10.50[c]
SD	11.79	5.55	3.37	3.02	3.16	2.87
F value	58.21					
P value	<0.0001*					

Significance level P<0.05, *significant

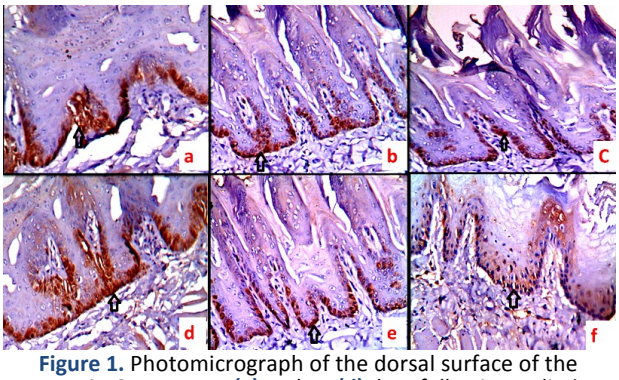

Figure 1. Photomicrograph of the dorsal surface of the tongue in Group I at 7 **(a)** and 14 **(d)** days following radiation showing disturbed architecture of basal cells. LC treated group II reveals slight alteration in basal cell architecture and preserved keratin tips over the lingual papillae at 7 **(b)** and 14 **(e)** days following radiation. LC & VE treated group III reveals normal appearance of the filliform papillae and normal epithelial thickness at 7 **(c)** and 14 **(f)** days following radiation. (H&E, ×200).

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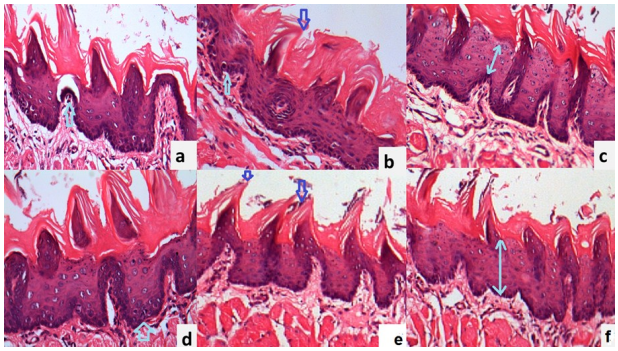

Figure 2. Photomicrograph of the dorsal surface of the tongue showing intense p53 staining in basal cells Group I at 7 days **(a)** and 14 days **(d)**. Decrease in p53 immunostaining is noted in group II at 7 days **(b)** and 14 days **(e)**, with marked decrease in group III at 7 days **(c)** and 14 days **(f)** (H&E, ×200).

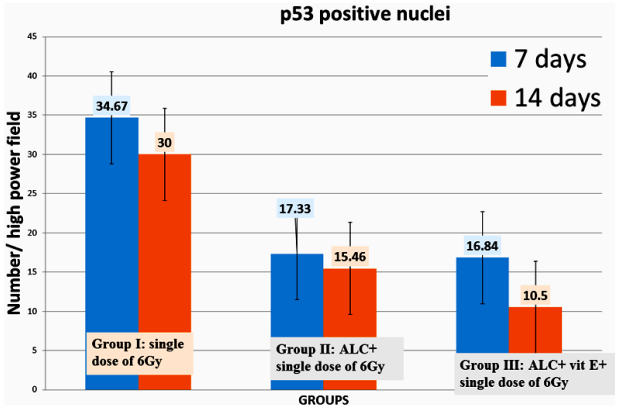

Figure 3. Column chart showing mean number of p53 positive cells/ high power (x400) field in different group.

DISCUSSION

L-carnitine possesses a strong antioxidant activity and suppresses the mitochondrial release of free electrons that generate free radicals [55]. Improvement of epithelial integrity after the administration of high-dose L-carnitine can be attributed not only to an improved cellular energy balance from improved mitochondrial fat burning but also to the favorable effect of LC on glucose utilization and cytokine metabolism [56]. There are many experimental studies reporting the protective effect of carnitine against the toxicity of irradiation and antineoplastic agents including doxorubicin and cisplatin [58].

The biological functions of LC go far beyond its role in the transport of fatty acids. Carnitine and its acetylated derivatives facilitate the β-oxidation and improve energy metabolism, minimize the toxic effects of free forms of long-chain fatty acids in and around mitochondria, protect the mitochondrial membranes and prevent permeability transitions, therefore, suppresses the release of free electrons that generate free radicals and cytochrome that activates caspases. LC protects against oxidative stress and reduces the apoptosis rate [55-57]. Regarding apoptosis, an increase in the apoptotic protein p53 after receiving radiotherapy is consistent with prior studies in animals, human cell lines, and intestinal crypts after treatment with chemotherapy and/or radiotherapy and is correlated to increased apoptotic activity which results in intestinal mucositis [59]. Down regulation of apoptotic proteins p53 with time at 14 days corresponding with improvement of the histological appearance. Remarkably, these findings correlate with the five-phase theoretical mucositis model suggested by Sonis (2004) [60].

CONCLUSIONS

LC and VE has shown positive effect in minimizing the epithelial atrophy of tongue mucosa after radiotherapy, which was emphasized by decreasing apoptotic activity in these tissues.

***Conflicts of interest*:** *Declared none.*

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