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Effect of coenzyme Q10 on radiation-induced fatigue in rats

Y. Ki[1], W. Kim[1*], Y. Kim[1], D. Kim[1], J. Bae[1], D. Park[1], H. Jeon[2], J. Lee[2], J. Lee[2], J. Nam[2]

[1]*Department of Radiation Oncology, Biomedical Research Institute, Pusan National University Hospital and Pusan National University School of Medicine, Busan, Korea*
[2]*Department of Radiation Oncology, Pusan National University Yangsan Hospital, Yangsan, Korea*

► ***Original article***

Corresponding author:
Dr. Wontaek Kim,
Fax: *+82 51 248 5747*
E-mail: *rokwt@hanmail.net*

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ABSTRACT

Background: Fatigue is a common side effect in cancer patients undergoing radiation therapy (RT). Radiation-induced fatigue affects the quality of life, but there is no definitive treatment option. In this study, the weight-loaded forced swim test was performed to assess the effect of coenzyme Q10 (CoQ10) on radiation-induced fatigue. ***Materials and Methods***: A total of 60 rats were divided randomly and equally into four groups: No swim, No RT, RT + placebo, or RT + CoQ10. The No swim, No RT, and RT + placebo groups received 1 mL of soybean oil daily for 14 days. The RT + CoQ10 group received 100 mg/kg of CoQ10 in soybean oil at the same times. Both RT groups were irradiated with 10 Gy on the 14th day of treatment. The swim test with sinkers weighing 10% of body weight was performed 24 h later in all animals except the No swim group. ***Results:*** The level of blood urea nitrogen (BUN) was significantly lower in the No swim than the other groups. The BUN level of the No RT group was significantly decreased compared with the RT + placebo group, but it did not differ from the RT + CoQ10 group. Swimming times to complete exhaustion were significantly longer in the No RT and RT + CoQ10 groups compared to the RT + placebo group (99.4, 105.9, and 75.7 s, respectively) (P<0.001). ***Conclusion:*** Supplementation with CoQ10 can prevent the decrease in endurance capacity caused by radiation.

Keywords: *Coenzyme Q10, radiation therapy, fatigue, rats.*

INTRODUCTION

Fatigue is one of the most common symptoms in cancer patients, and a common side effect of many anti-cancer treatments [1, 2]. Fatigue is associated with psychological stress, depression, anemia, pain, sleep disorders, poor nutrition, and decreased functional capacity [3]. During radiation therapy (RT), acute fatigue occurs in over 70% of patients, about 30% of whom may suffer from chronic fatigue after the completion of radiotherapy [4, 5]. Only about half of the patients with fatigue discuss this symptom with their physicians, and only about 25% receive any intervention [6].

Fatigue has been ignored, or underestimated, in cancer patients because major symptoms such as pain, nausea, and vomiting are considered the main concerns. However, radiation-induced fatigue is becoming a chief complaint in most cancer patients because it affects the quality of life adversely after the other main symptoms are controlled [2]. Although various approaches for the management of radiation-induced fatigue have been tried, such as group psychotherapy, physical exercise, and sleep along with exercise, effective therapeutic options remain limited [6].

Coenzyme Q10 (CoQ10) is a fat-soluble,

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vitamin-like substance also known as ubiquinone. The highest concentrations of CoQ10 are found in tissues with high-energy turnover such as brain, heart, liver, kidney, and muscle [7]. CoQ10 is a ubiquitous and indispensable compound in the respiratory chain of the inner mitochondrial membrane, and acts as an essential antioxidant, assisting in the regeneration of other antioxidants. CoQ10 increases the endurance capacity and decreases the sensation of fatigue after physical activity [8]. Administration of CoQ10 was demonstrated to be effective in controlling chemotherapy-related fatigue [9]. However, there has been no previous report of supplementation with CoQ10 for radiation-induced fatigue. The aim of the current study was to investigate the effects of CoQ10 on radiation-induced fatigue using the forced swim test in rats.

MATERIALS AND METHODS

Animals and CoQ10

A total of 60 adult male Sprague-Dawley rats, weighing 300–350 g, were used. The animals were housed in wire cages at a constant temperature of 22 ± 2°C, in a 12-h light/dark cycle. Rats were given standard laboratory chow and UV-sterilized water. After a 1-week adaptation period, rats were allocated randomly to the following groups of 15: No swim, No RT, RT + placebo, or RT + CoQ10. The No swim, No RT, and RT + placebo groups received 1 mL of soybean oil once daily through a feeding cannula for 14 d. The RT + CoQ10 group received the same volume of soybean oil containing 100 mg/kg of CoQ10 using the same protocol. Body weights were checked daily.

The experimental protocol was reviewed and approved by the institutional animal care and use committee at Pusan National University Hospital (No. PNUH 2013-053).

Irradiation

All rats were anesthetized with an intraperitoneal injection of 100 mg/kg ketamine hydrochloride on day 14 after feeding soybean oil with or without CoQ10. The RT + placebo and RT + CoQ10 groups then received a single 10 Gy whole body dose of irradiation using a 6-MV photon beam. Five rats were restrained by the tail in a prone position on a 1 cm-thick acrylic plate and covered by another plate with the same thickness. Radiation was administered simultaneously to all five rats at a 3 cm depth through anterior-posterior and posterior-anterior fields using a linear accelerator (Clinac 21EX, Varian Medical System, Inc., Palo Alto, CA, USA). The radiation dose rate was 1.06 Gy per minute.

Weight-loaded forced swim test

The all rats were pre-exposed to the test for 30 s 24 h before irradiation (namely 48 h before the test) to be familiarized to a forced swim. The animals in the three swim groups were tested using the procedure described in previous reports [10, 11]. The swim test was performed 24 h after irradiation based on a previous report that exploratory activities in rats were depressed significantly during the first 3 d after irradiation with a single dose of 10 Gy [12]. A steel cylinder, 40 cm in diameter and 60 cm high, was filled with 25˚C water to a depth of 50 cm so the rats could not touch the bottom with their tails or feet. Sinkers weighing about 10% of the body weight of each animal were tied to the tail in order to force the animals to work to stay afloat because rats without sinkers can float and rest in the water without swimming continuously. Each rat was individually placed into the water tank carefully. Swimming times to complete exhaustion were measured from the moment the animals were placed into the water until they ceased to struggle for 10 s and could not rise above the water surface to breathe [13]. The animals were then removed from the water and dried. There were no animal drowning deaths associated with this protocol.

Laboratory tests

The body weights of all animals were measured 1 h after the forced swim test. Blood samples were then taken for measurements of hemoglobin (Hb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine.

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Statistical analyses

Mean differences among the four groups were assessed by one-way analysis of variance followed by Bonferroni's multiple comparison test. Statistical analyses were performed using SPSS, version 22.0 (IBM, Chicago, IL, USA).

RESULTS

Laboratory findings

There were no significant differences in the blood levels of Hb, AST, ALT, and creatinine among the groups. The BUN level was significantly lower in the No swim group than the other groups. The BUN level in the RT + placebo group was significantly higher than the No RT group. There was no significant difference in the BUN levels between the No RT and RT + CoQ10 groups (P = 0.306). The RT + placebo group showed a higher BUN level compared to the RT + CoQ10 group (P = 0.008). The laboratory results are presented in table 1.

Body weights

Body weights increased daily in all animals, but were decreased after irradiation and/or swimming. The mean weight changes observed between before RT and after the forced swim test were +4.2, -3.2, -74.7, and -69.0 g in the No swim, No RT, RT + placebo, and RT + CoQ10 groups, respectively (figure 1). Irradiated animals showed significant weight loss compared with the two non-irradiated groups ($P < 0.001$). No significant difference in weight loss was observed between the two irradiated groups ($P = 0.108$).

Table 1. Effects of coenzyme Q10 and radiation on laboratory findings in rats.

Groups	Hb (g/dL)	AST (IU/L)	ALT (IU/L)	BUN (mg/dL)	Creatinine
No swim	15.8 ± 1.0	75.5 ± 15.5	52.8 ± 9.3	21.1 ± 3.4	0.44 ± 0.09
No RT	15.6 ± 1.0	78.1 ± 13.4	53.9 ± 14.1	26.7 ± 4.7*	0.46 ± 0.10
RT + placebo	15.0 ± 1.0	72.3 ± 14.8	51.7 ± 11.3	36.3 ± 6.3*/**	0.45 ± 0.10
RT + CoQ10	15.1 ± 1.0	75.1 ± 15.9	48.3 ± 11.6	30.3 ± 4.6*	0.42 ± 0.12

Data represent means ± SD (n = 15 per group).
*P < 0.05 compared with the No swim group
**P < 0.05 compared with the No RT group

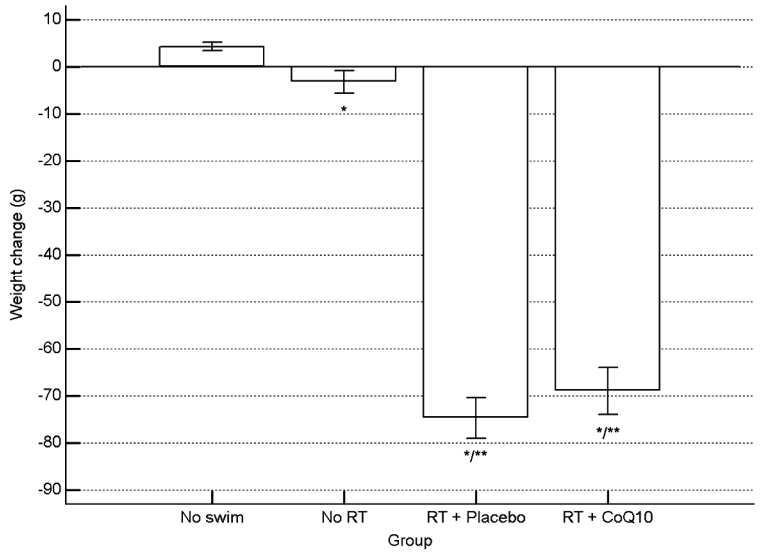

Figure 1. Weight changes between before irradiation and after the forced swim test in rats. Data are expressed as means ± SD (n = 15 per group). *P < 0.05 as compared with No swim group. **P < 0.05 as compared with No RT group.

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Weight-loaded forced swim test

As shown in figure 2, the RT + placebo group exhibited a significant decrease in swimming time as compared with the other groups. The mean duration of swimming until exhaustion was 99.4 s in the No RT group. The mean swimming time in the RT + placebo group was 75.7 s and showed a significant difference compared to the mean time of the No RT group ($P < 0.001$). The RT + CoQ10 group had a mean swimming time of 105.9 s which was significantly longer than the RT + placebo group ($P < 0.001$) and comparable to the No RT group ($P = 0.466$).

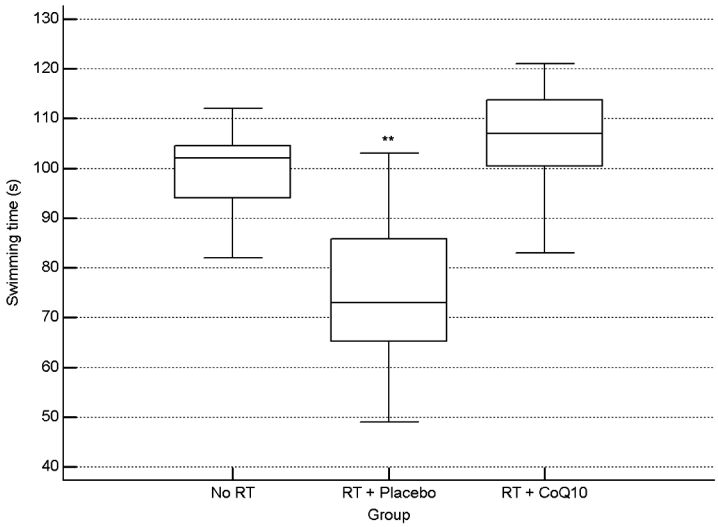

Figure 2. Effect of CoQ10 and radiation on swimming time to exhaustion in rats. Data are expressed as means ± SD (n = 15 per group). $^{**}P < 0.05$ as compared with No RT group.

DISCUSSION

Radiation-induced fatigue may be caused potentially by anemia, malnutrition, weight change, diarrhea, myelosuppression, stress, and depression [6]. However, the reasons for this fatigue, correlations with other factors, and prevalence are poorly understood [14]. Fatigue is defined as a loss of the capacity to generate force during exercise and can be classified into mental and physical fatigue [11]. Fatigue is a nonspecific and multidimensional symptom and generally manifests as a subjective sense of tiredness or decreased capacity of physical performance [6]. While a symptom checklist and physical performance test have been used in human studies to measure the intensity of fatigue, in animals, physical capacity tests such as the forced swim test, treadmill test, and wheel running test are used [11, 15].

The weight-loaded forced swim test was used in this study to compare the endurance capacity of rats, reflecting the degree of fatigue. The swimming time to complete exhaustion in the RT + placebo group, with a tail load of 10% of the rats' body weight, was significantly shorter than the No RT group. Whole body irradiation might decrease the animals' endurance capacity. Supplementation with CoQ10 significantly increased the swimming time of the irradiated rats, making them comparable to the No RT group.

BUN is the final product of protein and amino acid metabolism. After strenuous exercise, BUN level increases because of strong catabolic metabolism when the intensity is beyond a physical ability [16]. Therefore, BUN has been used as one of the sensitive indicators for evaluating endurance capability and physical fatigue of animals [11, 17]. An increased BUN level reportedly correlates with lower physical endurance [16]. In this study, BUN was increased in all groups tested with the weight-loaded forced swim test. In the No RT group, BUN also increased significantly compared with the No swim group ($P = 0.013$). The RT + placebo group

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showed the greatest increase in the BUN level of all groups. There was, however, no significant difference in the BUN level between the No RT and RT + CoQ10 groups. Therefore, supplementation with CoQ10 may have the potential to decrease the BUN level that is elevated after irradiation. The antioxidant effect of CoQ10 was also reported to decrease the post -exercise BUN level [11].

Significant weight loss was observed in the RT + placebo and RT + CoQ10 groups, compared with the No swim and No RT groups, indicating that CoQ10 had no beneficial effect on this parameter. Weight changes did not correlate with the swimming time to complete exhaustion in the two RT groups.

The levels of CoQ10 in organs decrease with age [18]. Many studies report that CoQ10 supplementation has various positive effects for cardiovascular diseases, neurodegenerative diseases, diabetes, and migraines [19]. A wide range of doses (60–600 mg/d) of CoQ10 are generally used, and a dose up to 2400 mg/d was used safely in a study on neurodegenerative disease [20]. For these reasons, CoQ10 doses up to 3000 mg/d in humans appear to be safe, and the administration of CoQ10 was well-tolerated in rats at doses up to 1200 $mg \cdot kg^{-1} \cdot d^{-1}$ [21, 22].

Various reports about the anti-fatigue effects of CoQ10 have appeared [8, 19]. Supplementation with CoQ10 increased oxidative phosphorylation within mitochondria and improved antioxidant protection during prolonged exercise [23]. Administration of CoQ10 improved the subjective feeling of fatigue, as well as physical fatigue during fatigue-inducing physical tasks [7]. Increased CoQ10 enhanced oxidative phosphorylation in mitochondria and consequentially improved exercise capacity [8]. The time to exhaustion was increased after both a single application of CoQ10 as well as chronic supplementation [8]. However, supplemental CoQ10 may not accumulate in tissues and its half -life in plasma is about 33 h [24]. Accordingly, CoQ10 has been generally administered daily over 1 to 4 weeks in previous researches to maintain a steady-state CoQ10 concentration [7, 8, 11]. In anti-fatigue studies, dosages of 60–100 mg/d of CoQ10 were usually used and showed favorable results. Based on these reports, we administered 100 $mg \cdot kg^{-1} \cdot d^{-1}$ of CoQ10 to rats for 14 d before irradiation, and the forced swim test was performed 24 h after irradiation.

In radiation therapy with photon, most of the therapeutic effect occurs indirectly through the reactive oxygen species, which are produced when ionizing radiation strikes water [25]. Nuclear DNA damage by the free radicals ultimately leads to tumor cell death. Previous reports suggested that concurrent administration of CoQ10 and RT should be discouraged because systemic CoQ10 might reduce the effectiveness of irradiation by scavenging free radicals [26]. However, the free radical-mediated DNA reaction is extremely fast and dissipates within only a few milliseconds [27]. Another report suggested that CoQ10 may be useful in adjuvant therapy for cancer [28]. Based on these results, supplementation with CoQ10 may be useful in preventing fatigue without interfering with the treatment when applied as an adjuvant therapy after completion of RT course.

In conclusion, the administration of CoQ10 improved the endurance capacity in irradiated rats. This result indicated that CoQ10 might have positive effects on radiation-induced fatigue. Further studies with larger numbers of animals and more varied schedules are required to confirm the ideal protocol for radiation-induced fatigue.

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

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