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Research Article

Investigation of the effect of vitamin C on the oxidative stress parameters induced by i-131 treatment applied in patients with hyperthyroidism

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Abstract

Aim or purpose: The radioactive I-131 (RAI) treatment is an adjuvant treatment option that increasingly is applied in hyperthyroidism, toxic nodular goitre and Grave's disease. The aim of this study is to investigate the possible radioprotective role of Vitamin C in I-131(RAI) treatment in hyperthyroid patients.

Material and methods: The patients who were undergone RAI treatment due to hyperthyroidism divided into 2 groups. While vitamin C was not given to the 1st group (24 patients) during RAI treatment, vitamin C in oral dose 1000 mg / day was given to the 2nd group (28 patients) throughout 1 week starting from 1 day before their treatments. Peripheral blood was drawn twice from the both groups before RAI treatment and on the 7th day after treatment. The oxidative stress parameters which are total antioxidant status (TAS), total oxidant status (TOS), ischemia modified albumin (IMA), malondialdehyde (MDA) were measured by obtaining serum samples, and their blood levels were measured biochemically with ELISA method by applying the 8-hydroxydeoxyguanosine (8-OHdG) kit protocols for DNA damage. The radioprotective effect of the Vit C was investigated as statistically by comparing the oxidative stress parameters that were obtained from both groups.

Results and conclusion: According to the results of our study, it was seen that vitamin C reduces the effects of oxidative stress that is caused by radiation, and it was thought that vitamin C supplementation is beneficial for patients to whom therapeutic radioactive materials was undergone.

Introduction

Radioactive I-131 therapy is treatment that can be applied to patients safely who have hyperthyroidism and do not benefit from antithyroid therapy or have drug toxicity developing [1,2]. However, besides that it has therapeutically effect on thyroid tissue I-131 can cause some undesirable effects on other organs of the body. One of the undesirable damages of radiation in biological systems is the genotoxic effects on DNA, and the other is the formation of reactive oxygen species (ROS) by interacting with water molecules that are abundant in the cell [3-5]. These effects have been revealed up to now, and that radioactive I-131 caused an increase in ROS formation in the body and the DNA damage, have been reported by various researchers [6,7].

ROSs are oxidant substances that generate during metabolic and physiological processes. The outer orbitals of ROS have one or more unmatched electrons and they are highly reactive. Because of these properties, they can easily turn them into unstable structures by reacting with the atoms and molecules that they meet. ROSs that are formed too much can damage many macromolecules such as carbohydrates, proteins, lipids, DNA and enzymes. Since they damage these structures, they can lead to many chronic diseases such as cancer, hyperlipidemia, diabetes mellitus, metabolic disorders, atherosclerosis, cardiovascular diseases and neurodegenerative diseases [8,9].

The most important ROSs that are formed are superoxide radical, hydrogen peroxide, hydroxyl radical and singlet oxygen. However, many oxidant substances can be taken into the body as exogenous. There are some anti-oxidant mechanisms in the body that can control the amount of ROS. Thus, oxidant and anti-oxidant mechanisms are in equilibrium in normal conditions. Oxidative stress is caused by the imbalance between the formation of ROS and their elimination by means of antioxidants [9,10].

Substances which may prevent or delay the oxidation that may occur and can trap and stabilize free radicals, are called antioxidants. Antioxidants that neutralize oxidants may be based on endogenous or exogenous. Endogenous antioxidants are divided into two classes as the enzymes and non-enzymes. Besides enzymatic antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), etc., non-enzymatic antioxidants such as melatonin, seruloplazmin, albumin etc. that are present in the body [10,11]. While exogenous antioxidants can be classified as vitamins, drugs and food antioxidants. Vitamin exogenous antioxidants are ascorbic acid (vitamin C), α-tocopherol (vitamin E), β-carotene and folic acid. Exogenous antioxidant intake may be beneficial to the body when endogenous antioxidants are not enough. Vit C, for example, is one of the most powerful antioxidants that is known [12]. Vit C is maintained in its reduced form by reaction with glutathione, which catalyzes by protein disulfide isomerase and

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glutaredoxins. Vitamin C is a reducing agent and can reduce and neutralize it, such as hydrogen peroxide [13,14].

Total antioxidant status (TAS) reflects the total effect of all antioxidants presenting in body fluids and total oxidant status (TOS) reflects the total effect of oxidants, and general antioxidant / oxidant status can be evaluated more easily by TAS and TOS measurements. The measurement of TAS reflects the overall anti-oxidant state in a living organism. This state gives more valuable information than individual measurements of these substances, and TOS and TAS measurements have been increasingly accepted [15-17]. Therefore, we thought that it will be appropriate to measure TOS for measuring all the oxidants that I-131 could form and to measure TAS for observing the effect of Vit C as an antioxidant.

Lipids are biomolecules that are most sensitive to the effects of free radicals. Malondialdehyde (MDA) occurs in the peroxidation of fatty acids containing three or more double bonds. Malondialdehyde (MDA) emerges in the blood and urine, and it is not a specific or quantitative indicator of fatty acid oxidation but correlates well with the degree of lipid peroxidation [19]. For this reason, malondialdehyde (MDA) measurement in biological material is used as an indicator of lipid peroxide levels [18-20].

ROS also causes structural changes by reducing the binding capacity of transition metals such as copper, cobalt and nickel at the N-terminal end of serum albumin, and consequently a new albumin called 'ischemia modified albumin' (IMA) emerges [21]. Besides ROSs, hypoxia and acidosis increase IMA formation. Because of this, since IMA is a nonspecific biomarker, besides it increases in coronary cases, its level may be increase in all cases that oxidative stress increase [22,23].

The most common oxidative damage of DNA is 8-hydroxylation of guanine base resulting in the formation of 8-hydroxy 2-deoxyguanosine (8-OHdg) molecule. 8-OHdG is commonly used as a biomarker to evaluate oxidative DNA damage in the body. It was found that the level of 8-OHDG increases in many clinical situations such as diabetes, cardiovascular diseases and cancer. It is also reported in the literature that systemic oxidative stress causes endothelial dysfunction [24-27].

On the other hand, when applying the I-131 whose therapeutic feature is often used, to the patients, there has not much been taken advantage of radioprotective agents until now. However, recently, it has been few studies reported that antioxidant vitamin applications may be beneficial [28-30]. For these reasons, more studies are needed to be done on radioprotection. Therefore, we firstly aimed to measure the effect of RAI treatment on the oxidative stress parameters TAS, TOS, IMA, MDA and 8-OHDG amounts in our study. As second, we wanted to investigate whether vitamin C supplementation as an exogenous antioxidant could help reduce the possible effects of oxidant I-131 therapy after the RAI treatment and in other words whether it could be a radioprotective agent.

Material and method

The 54 patients (37 female, 15 male, mean age 63 ± 12.49) who had been sent to Çanakkale Onsekiz Mart University Faculty of Medicine Nuclear Medicine Clinic for the RAI treatment due to the hyperthyroidism were included in the study as randomized. The approval form was read, and patients was ensured to sign by having them be informed about RAI treatment. In addition, a document showing that they were volunteer for the study was signed by volunteers by giving information about this study and by including only volunteers to the study. For this study, necessary approvals were received from both the local ethics committee and the ethics committee of the Ministry of Health. Patients that were included in the study were divided into two groups as Group 1 (24 patients) and group 2 (28 patients). While vitamin C was not given to the first group during RAI treatment it was given to the second group. Vit C was started to give to the second group 2 days before the RAI treatment and was ensured to be used by them in 1000mg / day dose for 7 days. 5 cc peripheral blood was drawn from both groups before RAI and Vit C were initiated.Also, 5 cc peripheral blood was drawn from both groups on the 5th day after the treatment of RAI (when 2nd group was using Vit C). The serum of the blood had been separated by centrifugation at 1000 xg for 15 min at +4 ° C and stored at -20 ° C until the day of operation. The parameters of total oxidant status (TOS), total antioxidant status (TAS), ischemia modified albumin (IMA), malon dialdehyde (MDA) and the 8 hydroxydeoxyguanosine (8-OHdg) for DNA damage were studied in the Biochemistry Laboratory of Çanakkale Onsekiz Mart University Medical Faculty by ELISA method in accordance with kit protocols. The radioprotective effect of Vit C was investigated by statistically by comparing all values that had been obtained from both groups.

Statistical evaluation: The data of the study was transferred to the SPSS 15.0 statistical program in electronically and the data control and analysis were done by using this program. Wilcoxon significance test for dependent groups and Mann-Whitney U test for independent groups was used in statistical comparisons. The value of $p < 0.05$ was accepted as statistically significant.

Results

The demographic characteristics of 52 patients who were included in the study were summarized in Table 1. There was no statistically significant difference between group 1 and 2 in terms of age, gender, RAI dose and smoking status.

When compared TOS, TAS, IMA, MDA and 8-OHdg values obtained from Group 1 without Vit C and group 2 with Vit C in patients with hyperthyroidism treated with radioactive I-131 before and after treatment, the findings of each parametric study were as follows, respectively:

When Table 2-A examined, no difference was observed between TOS values obtained before RAI treatment ($p = 0.620$) and after RAI treatment ($p = 0.985$) in Group 1 and Group 2 according to the Mann-Whitney test results. When the TOS values were examined in both groups before and after RAI treatment, it was determined that there was increase in TOS values after RAI treatment due to oxidant effect of RAI treatment. It was observed that there was a statistically significant increase ($p = 0.005$) in Group 1 who did not use Vit C, but there was not a significantly increase ($p = 0.092$) in Group 2 who used Vit C supplement. Therefore, it was concluded that the increase of total oxidant status was less in group 2 due to the antioxidant effect of vitamin C supplementation.

When Table 2-B was examined, it was not observed any difference between the TAS values before RAI treatment (p=0.0609) and after RAI

Table 1. Demographic characteristics of study population

Demographic characteristics	Group 1 (n=24)	Group 2 (n=28)	p* value
Age (Yrs)	63.08 ±12.95	62.93 ± 12.33	0.920
Cinsiyet (male)	25%	32.1%	0.575
I-131 treatment dose (mCi)	17.29±2.54	16.25±2.92	0.212
Smoke	29.2%	28.6%	0.963

p*: Mann-Whitney U test

treatment (p = 0.861) in Group 1 without Vit C supplement and Group 2 with Vit C supplement according to the results of the Mann-Whitney test. When TAS values of Group 1 and 2 before and after RAI treatment were examined, it was observed that there was a decrease in TAS values after RAI treatment, but due to the antioxidant effect that was provided by Vit C supplement, whereas this decrease was statistically significant (p = 0.002) in Group 1, it was seen that it was not significant in Group 2 (P = 0.199). Therefore, it was concluded that it caused much less decrease in TAS due to the antioxidant effect that was provided by Vit C support. μmol Trolox Eq/L.

The IMA values that were obtained before and after RAI treatment in both groups are seen in Table 2-C. While it was not observed any statistically significant difference between the IMA values before treatment (p = 0.085) and the values after treatment (p = 0.368) between the groups, it was seen that the IMA values increased in both groups after RAI treatment, and the increase was statistically significant in both groups (Group 1 p = 0.001 - Group 2 p<0.001). When these results were interpreted, it was concluded that vitamin C supplements could not prevent the formation of IMA at these doses.

When Table 2-D was examined, it was determined that there was no significant difference (p = 0.378) between MDA values before RAI treatment between groups according to the Mann-Whitney test results, but there was a significant difference between MDA values after RAI treatment (p = 0.004). When the MDA values of Group 1 and Group 2 were examined separately before and after the RAI treatment, due to the antioxidant effect provided by Vit C supplement it was observed that there was an increase in the MDA values after RAI treatment in both groups, but this increase was statistically significant in Group 1 who did not use Vit C (p = 0.002) but not significant in Group 2 who used Vit C supplement (p = 0.255). Therefore, it was concluded that RAI treatment resulted in an increase in MDA values, but the antioxidant effect of vitamin C supplement reduced the amount of MDA after RAI treatment.

Lastly, when Table 2-E was examined, it was not observed any difference between groups in terms of 8-OHDG values both before RAI treatment (p = 0.582) and after RAI treatment (p = 0.066) according to Mann-Whitney test results. When the 8-OHHG values of Group 1 and Group 2 were examined separately before and after the RAI treatment, there was an increase in the 8-OHDG values after RAI treatment in both groups, but due to the antioxidant effect provided by Vit C supplement it was observed that this increase was statistically significant in Group 1 who did not use Vit C (p <0.001), but not significant in Group 2 who used Vit C supplement (p = 0.145). For this reason, due to its antioxidant effect, it was concluded that Vit C supplement reduced the amount of 8-OHDG formation after RAI treatment.

Discussion

Radioactive I-131 (RAI) radionuclide is used increasingly in the treatment of both benign and malign thyroid diseases [1-2]. As is known, radioactive I-131 accumulates in the thyroid tissue and causes

Table 2-A. TOS values obtained before RAI treatment and after RAI treatment.

Group	Before RAI Treatment Total Oxidant Status(TOS) (μmol H_2O_2 Eq/L)		After RAI Treatment Total Oxidant Status(TOS) (μmol H_2O_2 Eq/L)		
	mean±SD	median(min-max)	mean±SD	median(min-max)	p*
Group 1 Vit C negative	6.701±2.933	6.600(1.90-11.98)	9.518±6.851	7.900(2.37-32.56)	**0.005**
Group 2 Vit C positive	7.027±2.699	6.915(2.30-11.60)	8.902±5.050	7.650(2.74-23.65)	0.092
p**	0.620		0.985		

p* : Wilcoxon Signed Ranks Test
p** : Mann-Whitney U Test

Table 2-B. TAS values before RAI treatment and after RAI treatment

Group	Before RAI Treatment Total Antioxidant Status(TAS) (μmol Trolox Eq/L)		After RAI Treatment Total Antioxidant Status(TAS) (μmol Trolox Eq/L)		
	mean±SD	median(min-max)	mean±SD	median(min-max)	p*
Group 1 Vit C negative	0.979±0.254	0.920(0.62-1.53)	0.746±0.220	0.780(0.24-1.10)	**0.002**
Group 2 Vit C positive	0.998±0.352	0.940(0.47-1.96)	0.892±0.253	0.895(0.41-1.66)	0.199
p**	0.861		0.060		

p* : Wilcoxon Signed Ranks Test
p**: Mann-Whitney U Test

Table 2-C. IMA values obtained before and after RAI treatment

Group	Before RAI Treatment Ischemia Modified Albumin(IMA) (Absorbance Units)		After RAI Treatment Ischemia Modified Albumin(IMA) (Absorbance Units)		
	mean±SD	median(min-max)	mean±SD	median(min-max)	p*
Group 1 Vit C negative	0.463±0.075	0.472(0.287-0.578)	0.561±0.099	0.551(0.399-0.874)	**0.001**
Group 2 Vit C positive	0.469±0.084	0.482(0.329-0.616)	0.569±0.065	0.588(0.411-0.672)	**p<0.001**
p**	0.085		0.368		

p* : Wilcoxon Signed Ranks Test
p** : Mann-Whitney U Test

Table 2-D. MDA values before and after RAI treatment

Group	Before RAI Treatment MDA (Malondialdehyde) (ng/ml)		After RAI Treatment MDA (Malondialdehyde) (ng/ml)		
	mean±SD	median(min-max)	mean±SD	median(min-max)	p*
Group 1 Vit C negative	1.919±0.720	1.770 (0.84-3.35)	2.697±1.360	3.370 (1.33-6.25)	**0.002**
Group 2 Vit C positive	1.863±1.098	1.590 (0.75-5.12)	2.108±1.178	1.725 (0.74-4.77)	0.255
p**	0.378		**0.004**		

p* : Wilcoxon Signed Ranks Test (Wilcoxon önemlilik testi)
p**: Mann-Whitney U Test

Table 2-E. 8-OHDG values both before RAI treatment and after RAI treatment

Group	Berfore RAI Treatment 8-OHdG (8-hydroxy-2'-deoxyguanosine) (ng/ml)		After RAI Treatment 8-OHdG (8-hydroxy-2'-deoxyguanosine) (ng/ml)		
	mean±SD	median(min-max)	mean±SD	median(min-max)	p*
Group 1 Vit C negative	0.166±0.182	0.124(0.082-0.987)	0.192±0.114	0.156(0.056-0.548)	**p<0.001**
Group 2 Vit C positive	0.160±0.166	0.127(0.082-0.987)	0.173±0.115	0.136(0.091-0.575)	0.145
p**	0.582		0.066		

p* : Wilcoxon Signed Ranks Test
p**: Mann-Whitney U Test

cell death in most of the thyroid cells due to its cytotoxic and apoptotic effects under favor of its beta-negative rays. However, this highly effective treatment can cause some undesirable effects since there occurs ionizing radiation in other organs of the body. In biological systems, one of these undesirable damages of radiation is the genotoxic effects on the DNA and the other is the formation of ROS by interacting with the water molecules that are abundant in the cell. Increased ROS in the body due to ionizing radiation can damage important biomolecules such as DNA, lipids and proteins. It has been reported by many researchers that the damage occurring in these molecules plays an important role in both onset and progression of many of chronic diseases such as cancer, cardiovascular diseases, metabolic diseases and gastrointestinal diseases [31-33].

In a meta-analysis study that they conducted, Einor *et al.* reported that there is a strong relationship between ionizing radiation and oxidative stress, but the rates of ionizing radiation exposure of biological materials and tissues are highly heterogeneous [34]. These findings are consistent with some species being apparently and negatively impacted by ionizing radiation, while the others are not, or even showing evidence consistent with adaptation to radiation by having positive antioxidant responses at high levels of radiation.

That the ionizing radiation cause an increase in oxidants in the body is a well-known fact in the literature [34-37]. The oxidant substances already form during the biological cycle in the body, but the formation of oxidant substances can increase by such factors as hypoxia, acidosis, ionized radiation and so on. These increases may be inadequate depending on the amount resulting in antioxidant defense system of the body can neutralize. Therefore, we planned this study to investigate the oxidative stress increase of ionizing radiation I-131 in hyperthyroid patients and the radioprotective effect of Vit C, a potent antioxidant substance.

The overall antioxidant / oxidant status in body fluids can be more easily assessed by TAS and TOS measurements. Under normal conditions, oxidant and antioxidant state are in equilibrium. For this reason, it was important that the effect of ionizing radiation, strong oxidizing agent known to break this balance in the body, and the effect of Vit C which could neutralize its oxidant effect on TAS and TOS values. Because, when our study results were evaluated, it was determined that the increase of TOS values after RAI treatment due to oxidant effect of RAI treatment. However, while this increase was statistically significant ($p = 0.005$) in Group 1 who did not use Vit C, but not significant ($p = 0.092$) in Group 2 who used Vit C. Therefore, the antioxidant effect of vitamin C supplementation was thought to reduce the TOS levels that occur.

Also, it was observed that there was a decrease in TAS values after RAI treatment, but it was statistically significant in Group 1 ($p = 0.002$) but not in Group 2 ($p = 0.199$) due to the antioxidant effect provided by Vit C supplement. For this reason, it was concluded that it causes less decrease in Total Antioxidant Status due to the antioxidant effect provided by Vit C supplement.

MDA is used as an oxidative stress marker since the increase in the amount of ROS increases the MDA level. It was reported in many studies that oxidative stress agents increase MDA levels [38-40]. We also determined an increase in MDA levels after treatment in both groups to whom I-131 treatment was applied in our study. But, we observed that this increase in Group 2, which we gave Vit C supplement during I-131 treatment, was less than that of Group 1, which we did not give Vit C supplement. Starting from this result, we thought at this point that vitamin C produced radioprotection by partially reducing MDA formation.

While, as reported in many studies, IMA which is an indicator of ischemia and oxidative stress may increase especially in cardiac ischemia, it is understood from the literature that it may also increase in many noncardiac diseases [41,42]. Reddy VS *et al.* identified the relationship between IMA and thyroid diseases in a meta-analysis and they reported that IMA values increase in both hypothyroidism and hyperthyroidism and can be easily measured as an oxidative stress parameter in thyroid dysfunctions [43]. In our study results, it was seen that Vit C support was not able to prevent IMA formation. This result that was obtained was interpreted in the way that IMA formation increased depending on both the oxidant effect of hyperthyroidism in the early stages of I-131 treatment and the oxidative effect of I-131 and Vit C could not have

an adequate antioxidant effect at this dose. While antioxidant support studies during ionizing radiation applications have not been done so much up to now, our results suggest that these studies should be done at different doses. On the other hand, the most common oxidative damage of DNA is 8-hydroxylation of guanine base resulting in the formation of 8-hydroxy 2-deoxyguanosine (8-OHdg) molecule [44]. 8-OHdG is commonly used as a biomarker to evaluate oxidative DNA damage in the body. Numerous studies implicated excessive reactive oxygen species generation can damage to macromolecules (such as DNA and protein), and lead to 8-OHdG formation [26,45]. Enhanced 8-OHdG levels were found in patients with diabetes, cardiovascular disease and cancer [46,47].

There are quite few and contradictory publications about this subject in the literature. There are studies reporting that antioxidant vitamin applications may be beneficial as well as studies reporting that they are not beneficial. For example, while Huang *et al.* reported that Vitamin E and Vitamin C applications did not affect the formation of 8-OHDG in non-smokers [29], Hakim *et al.* reported that the use of antioxidant green tea reduced the formation of 8-OHDG in smokers [48]. In addition, Xiao *et al.* reported that 6-O-Palmitoylscorbate-l which is derivation of vitamin C prevents the oxidative effects of radiation [49]. Maneshet *et al.* [50] reported that the dose response for radiation-induced extracellular 8-oxo-dG was non-linear and that intracellular dNTPs were an important source of radiation-induced extracellular 8-oxo-dG. While Szumiel *et al.* [32] have reported that ionizing radiation can directly cause DNA genomic changes, as well as it can cause genetic damage through epigenetic alteration of Reactive Oxygen Species (ROS) which are caused by ionizing radiation. Therefore, it is necessary to follow the formation of oxidative resources that can lead to many diseases and to do studies for prevention. According to our study results which is one of the rare studies in which antioxidant supplement is given to person during ionizing radiation applications, Vit C supplement decreases the amount of 8-OHDG after RAI treatment due to antioxidant effect.

In conclusion, when we examined 5 important parameters that could be occurred by the free radicals occurring after RAI treatment in our study, it was seen that RAI treatment increased the formation of TOS, MDA, IMA and 8-OHDG statistically significant. On the other side, it was found that the application of Vitamin C with RAI treatment reduced TOS, MDA and 8-OHDG formation, reduced TAS status as positively but it did not have a significant effect on reducing IMA formation. Therefore, it is thought that such studies should be carried out in wider series and that vitamins proved to have radioprotective effect as it is in our study may be beneficial for treatments that are applied by using radiation.

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Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

All authors contributed equally to this work, read and approved the final manuscript.

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