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Original

The efficacy of melatonin against radiotoxicity of iodine-131 and its response to treatment in hyperthyroid patients: a randomized controlled trial

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Abstract

Background: Since melatonin is a non-toxic compound with proven radioprotective effects, we aimed to investigate its efficacy in an in-vivo setting in hyperthyroid patients who are treated with iodine-131. This double-blind placebo-controlled study was conducted on hyperthyroid patients referred to nuclear medicine centers in Babol, Iran. We excluded patients suffering from hypertension treated with warfarin, autoimmune diseases, genetic diseases, cancers, smokers, chemical wounded, radiology and radiotherapy workers, and those who were treated with chemotherapy agents. Patients were randomly assigned to receive a capsule containing 300 mg of melatonin powder or a placebo. Just before receiving iodine-131, blood samples were taken from individuals. All 52 female patients received 10 to 20 mCi iodine-131 for treating hyperthyroidism. A second blood sample was taken one hour after the administration of iodine-131.

Material and methods: To determine the chromosomal damages before and after receiving radioiodine, we performed the cytokinesis-block micronucleus assay. Also, at phase 2, 6 months follow-up was performed, in which patients' positive responses to treatment were compared.

Results: The findings of this study indicate that the difference in micronucleus formation between the placebo and melatonin groups is not significant. However, a significant difference in the 6 months follow-up revealed that 61.5% and 85.7% of patients had a positive response to treatment in the placebo and melatonin groups, respectively.

Conclusions: As one of the first studies dealing with the human in-vivo assessment on the radioprotective effects of melatonin, it was concluded that melatonin has a non-significant positive impact on reducing the rate of chromosomal damages in hyperthyroid patients treated with iodine-131. Nevertheless, the outcome of treatment was significantly higher by melatonin compared to the placebo group.

KEY words: hyperthyroidism; melatonin; radiation

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Introduction

Iodine-131 therapy is widely used to treat hyperthyroidism, which has turned into the treatment of choice for reversible hyperthyroidism [1]. However, a recent increase has been reported in the overall incidence of cancer among patients with hyperthyroidism that had been treated with radioactive iodine [2]. Chromosomal damages in peripheral lymphocytes have also been reported in patients with Graves' disease treated with iodine-131 [3]. Ionizing radiations interact with biological systems and cause the formation of free radicals or production of reactive oxygen species (ROS), which attack different cellular components, including DNA, membrane proteins, and lipids, leading to severe cell damages [4]. The antioxidant defense system could control the influx of ROS, which involves enzymatic and non-enzymatic components. The antioxidant system consists of antioxidant molecules with low molecular weight, such as glutathione, melatonin, vitamin E, folic acid, and different antioxidant enzymes [5].

Since the cell damage caused by radiation has been primarily attributed to the harmful effects of free radicals, molecules with free radicals scavenging properties will be especially useful as a radiation protector [6, 7]. Various radio-protectors have been made to increase the therapeutic index of ionizing radiation that selectively reduces the cytotoxic effects of normal tissues [8] However, most of them cause serious side effects, and some are toxic at doses required for radiation protector [9].

It has been shown that melatonin can be an immune-stimulant [10, 11] and an antioxidant [7, 12, 13]. Melatonin acts in a synergistic mechanism as a direct scavenger of free radicals (14) and an indirect antioxidant through stimulating activities on the performance of antioxidant enzymes and by inhibitory activity on the function of pro-oxidant enzymes [6]. Also, due to its compact size and high lipophilic feature, melatonin easily passes through the membrane and reaches all cellular biological components [15]. The results of numerous studies suggest that acute and chronic toxicity due to melatonin is minimal [6, 7].

Chromosomal abnormalities can be assessed merely by examining the number of micronuclei [by Micronuclei (MN) method] in dividing cells that have been stopped in the cytokinesis phase, which is a numeric or structural index for chromosomal changes [16, 17]. Peripheral blood lymphocytes are circulating throughout the body, including the thyroid, which will experience in vivo chromosomal damages [18, 19]. Therefore, examining the micronuclei in the peripheral blood lymphocytes can be used as a real "biological dosimeter" for exposure to radiation of patients who receive radiation therapy [20].

Although many in-vitro studies have shown that human blood lymphocytes treatment with melatonin can reduce the number of micronuclei induced by gamma radiation [6, 7], the effectiveness of this treatment as in-vivo is still being investigated.

Given the increasing use of radioactive iodine to treat hyperthyroidism, investigation to find a suitable radiation protector to reduce radiation-induced chromosomal damages in the body would be useful. Since melatonin is a non-toxic substance and has been proven to have radioprotective effects, this study aimed to assess the radioprotective effect of melatonin against chromosomal damage caused by iodine therapy in peripheral blood lymphocytes using MN assay also a 6 months follow up was performed which patients' response were compared.

Material and methods

Design

This double-blind placebo-controlled parallel study was conducted on 60 women with equal randomization. We have used simple random allocation to distribute patients in groups to minimize selection bias, and the sequence generation or allocation concealment steps and the implementation step were done by different persons. Consent has been obtained from each patient after a full explanation of the purpose and nature of all procedures used. The mean age of participants was 46.01 ± 14.66 and diagnosed with hyperthyroidism who have been referred to 2 nuclear medicine centers (Beheshti and Alborz) in Babol, Iran, to be treated with iodine-131. The MN assay of samples was done in The Cellular and Molecular Biology Research Center, Babol University of Medical Sciences, Babol, Iran. The MN data of 8 participants were missed because their sample was destroyed and did not yield analysis. Finally, we had 52 patients, 24 in the placebo and 28 patients in the study groups for MN analysis. However, in 6 months follow up, the data of 54 patients have obtained which 26 of them were in placebo and 28 in the melatonin group. Individuals with hypertension and those treated with warfarin, those who have autoimmune diseases, genetic diseases and cancer, smokers, chemical wounded, radiology and radiotherapy workers, and those treated chemotherapy agents were excluded from the study. Before starting the study, informed consent was obtained from all participants, which was set according to the guidelines by the National Committee for Ethics in biomedical research. This study has been registered in the Iranian Registry of Clinical Trials (IRCT); registry No: IRCT2014090419045N1, and we did not any important changes to methods after trial commencement. The investigation was approved by the Babol University of Medical Sciences ethical committee.

All patients using methimazole to control hyperthyroidism discontinued their medication seven days before radioiodine therapy. The initiation time for intervention in all patients was considered from 8 to 9 am.

Melatonin powder was prepared from Pure Bulk Company (USA) and was placed in a capsule under sterile conditions. A total of 30 capsules containing 300 mg of melatonin and 30 placebo capsules containing starch were prepared, and the capsules were blindly coded by an expert pharmacologist. One hour before the administration of iodine-131, a capsule containing 300 mg of melatonin or placebo was administered orally to patients on a random basis. One hour later, immediately before administration of iodine-131, an initial blood sample as the T (1) was taken from patients, and the second blood sample as T (2) was taken one hour after receiving iodine-131. In this period, all patients were clinically monitored, and side effects known for melatonin such as a headache, dizziness, nausea, and lethargy were recorded, if occurred.

Outcomes

From each sample, 500 microliters of whole blood were added to 4.5 mL of the culture medium RPMI 1640 (Gibco, USA), which contained 10% fetal bovine serum, 0.1 mL/5 mL phytohemagglutinin (Gibco, USA), antibiotics (penicillin 100 IU/mL, streptomycin 100 μg/mL) and 2 mM glutamine (Sigma, USA). The cultures were placed in the incubator under 37 ± 1 °C and 5% CO_2 conditions. Cytochalasin B (Sigma, USA) at a concentration of 6 μg/mL

was added to the medium after 44 hours. After 72 hours of incubation, the cells were isolated by centrifuging and re-suspended in the cold potassium chloride at a concentration of 0.075 M for 8 minutes at 1500 g. Then, they were washed three times with the fixator solution (containing methanol and acetic acid at a ratio of 1:5). The fixed cells were then spread on perfectly clean slides, dried for 24 hours at room temperature, and then stained by Giemsa (10%). The slides were examined with a magnification of 1 000 times to count the number of micronuclei in binucleated cells fixed in cytokinesis that their cytoplasm had been preserved entirely. To be considered as a micronucleus, those with cell diameters of 1/16 to 1/3 of the main cell nucleus, not connected to the main nucleus or had no overlapping, were counted. For each patient, 1000 binucleated cells were counted in each of the samples T (1) and T (2), and the number of micronuclei was recorded.

Blood samples from 8 patients who participated in the study were destroyed in the process of cell culture or staining. Finally, the counting was done on blood samples from 52 patients.

Data analysis was performed by paired sample t-test comparing mean MN before and after iodine therapy within groups. Independent samples t-test was done for comparing the quantity of MN between two study and placebo groups, respectively. The p values lower than 5% were considered as significant for this study, and the results were presented at a 95% confidence interval.

The sample sizes of 23 in each group achieve 91.25% power to reject the null hypothesis of equal means when the population means the difference is $\mu 1 - \mu 2 = 9.0 - 10.0 = -1.0$ with a standard deviation for both groups of 1.0 and with an alpha of 0.05 using a two-sided two-sample equal-variance t-test. After the dropout rate of 20%, the inflated sample size was determined as 29 patients.

As the second outcome, the patients were followed up by an endocrinologist 6 months after treatment, and the response to treatment was assessed among them. Patients with euthyroidism or hypothyroidism state were considered as a positive response to treatment, and those with hyperthyroidism were considered as treatment failure.

Results

From 60 included patients, the MN data of 8 participants were missed because their sample was destroyed and did not yield analysis. Finally, we had 24 in the placebo and 28 patients in melatonin groups for MN analysis, but our 6 months follow-up, the data of 26 patients of the placebo, and 28 patients in the melatonin group were analyzed. Patients who received placebo capsules before radioiodine therapy called the "Placebo" group and patients who received melatonin called the "Melatonin" group. The average age in the groups was 46.82 ± 12.40 and 44.62 ± 15.7, respectively. The average iodine-131 dosage received by the placebo group patients was 12.70 ± 3.59 mCi, while the dosage for the melatonin group accounted for 13.17 ± 3.31 mCi. There was no significant difference between the 2 groups at the significance level of 95% (p = 0.807). The average numbers of micronucleus before treatment with iodine-131 for placebo and melatonin groups were as 5.87 ± 3.59 and 5.50 ± 2.86, respectively (p = 0.677). The average numbers of micronuclei after treatment for placebo and melatonin groups were also as 10.13 ± 4.85 and 9.96 ± 5.34, respectively (p = 0.910). Typical micronucleated binucleate cells are shown in Figure 1.

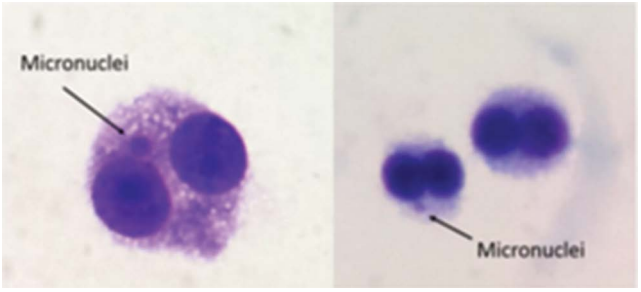

Figure 1. Typical binucleated lymphocytes with micronuclei in patients who received iodine-131 in the placebo group

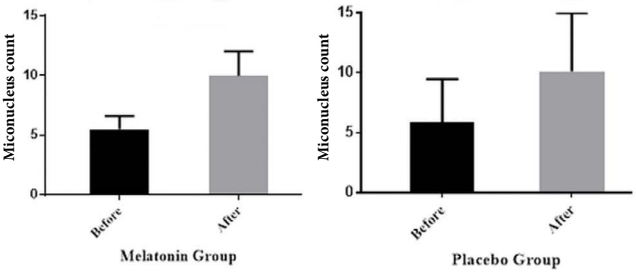

Figure 2. Average number of cells with micronuclei per 1000 cells counted for patients with melatonin (right) and placebo (left) groups before and after treatment with iodine-131

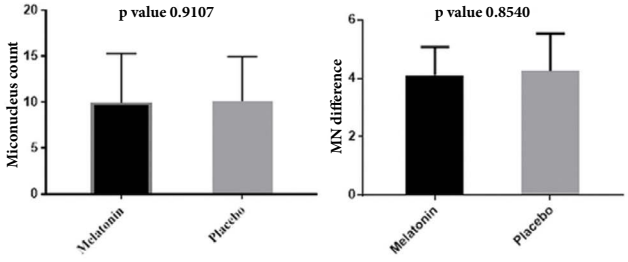

Figure 3. The mean (right) and ΔMN (differences between the number of micronuclei before and after treatment with iodine-131) (left) per 1000 cells counted for patients of melatonin and placebo groups

The data on the micronuclei count before treating with iodine-131 and after the treatment is shown in Figure 2 for both groups. According to this chart, treatment with iodine-131 in both groups has increased the number of micronuclei. In both groups, the difference between the number of micronuclei before and after treatment with iodine-131 is significant (Placebo group: $p < 0.0001$; Melatonin group: $p < 0.0001$).

Figure 3 shows the comparison of MN in 2 groups after iodine therapy also MN, which represent the difference in the number of micronuclei before and after treatment with iodine-131 in the 2 placebo and melatonin groups. As shown in Figure 3, MN is 4.25 ± 3.05 for the placebo group, and 4.10 ± 2.51 for the

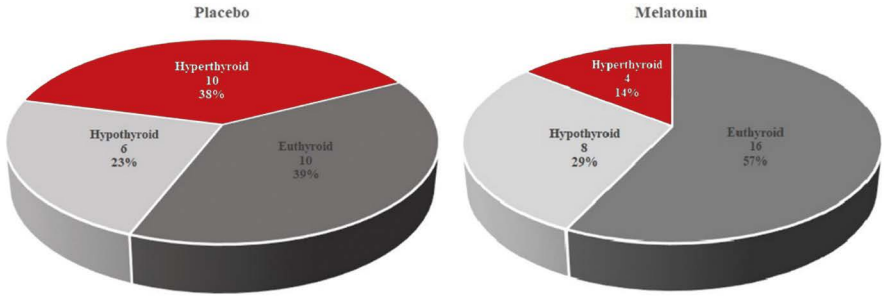

Figure 4. The treatment outcome in placebo and melatonin groups in a 6 month follow-up

melatonin group. However, there was no statistically significant ($p = 0.854$).

The patients participating in the trial were monitored clinically in the intervening period until the end of the treatment process for 2 hours. Eight subjects in the placebo group (33.33%) and nine patients in the melatonin group (29.0%) experienced the above complications. It should be noted that none of the patients experienced an acute symptom requiring remedial action.

Figure 4 shows the treatment outcome in the placebo and melatonin groups in separation. The information showed that 62% and 86% of patients had an excellent response to treatment in the placebo and melatonin groups, respectively. The results of the chi-square test showed that the difference in treatment outcome in the 2 groups was statistically significant ($p = 0.043$).

Discussion

Previous studies, which had been performed on in-vitro human and animal models, have shown that melatonin can be useful in reducing radiation-induced genotoxic damages [9, 21–30]. The current trial was carried out for the first time in the in-vivo environment and human subjects.

Data from this study indicate that treatment with iodine-131 at doses of 10 to 20 mCi significantly induces genetic damages in patients' blood lymphocytes. The doubled number of micronuclei in samples after administration of iodine was an appropriate marker for this hypothesis. Gil et al. [31] studied the DNA damages by the Micronuclei method in peripheral lymphocytes of patients with thyroid cancer after treatment with iodine-131. The number of micronuclei in cells from patients significantly increased one month after the treatment. Ballardin et al. [32] reported the 4-fold increase in the number of micronuclei in the seventh day after treatment in patients who had received therapeutic doses of iodine-131. However, the number of micronuclei then slowly fell and reached the baseline at day 180 after the treatment. In the three-month follow-up of hyperthyroid patients treated with iodine-131, Gutiérrez et al. [33] showed that the number of micronuclei in blood lymphocytes of patients would increase after treatment with iodine-131 increases, which is dose-dependent. Dardano et al. [34] also found in their study that administrating iodine-131 to treat hyperthyroidism in patients would cause a significant increase in the number of micronuclei in peripheral blood lymphocytes, which gradually decreased after 21 days and reached to the baseline at day 90 after the treatment. The increasing trend in the number of micronuclei as our study has been seen in all the mentioned previous studies. The differences in the increase in various studies may be explained due to different doses of iodine. According to these results, one can say that the micronuclei test can be used as a valuable endpoint and sensitive method for the biological study of iodine-131 radiation to assess the genetic damages in patients.

Iodine-131 is a useful radionuclide for the treatment of hyperthyroidism, but it has been reported that iodine therapy may increase the risk of secondary cancers due to genotoxic effects. Metso et al. observed a significant increase in the incidence of secondary cancers in the 10-year follow-up of patients who had received iodine-131 to treat hyperthyroidism [2]. The research carried out by Iyer et al. [35] suggests that the incidence of leukemia significantly increased in patients after treatment with iodine-131. This finding was also seen similarly in Sawka et al. study [36].

Two-third of chromosomal damages caused by ionizing radiations are created by generated free radicals. Due to the ability to collect the free radicals, antioxidants are capable of reducing adverse effects of ionizing radiation on living systems, including chromosomal damages [37]. Melatonin efficiency, as a naturally occurring compound in the human body, has been reviewed and approved regarding radiation protection in numerous studies. In this study, the number of micronuclei in the group receiving melatonin decreased compared to the group receiving a placebo. A significant reduction of chromosomal damages caused by gamma rays in the presence of melatonin had been seen in human and animal studies. Vijayalaxmi et al. [27] treated the human peripheral blood cells in the in-vitro environment with melatonin. The cells were then irradiated with gamma rays. Lymphocytes being in the melatonin-rich environment before exposure showed a significant and dose-dependent reduction in the frequency of radiation-induced chromosome damage compared to control cells. In another study by Reiter et al. [28], some volunteers received a single oral dose of 300 mg melatonin, and their blood samples were collected before receiving melatonin as well as 1 and 2 hours after receiving melatonin. Samples collected in the in-vitro environment were irradiated by cesium-137 gamma-ray at a dose of 150 cGy and were then studied regarding chromosomal abnormalities and micronucleus. During observations, the highest concentration of melatonin was seen in human serum and leukocytes in samples collected one hour after oral administration of melatonin. Consequently, a further reduction was seen in the incidence of genetic abnormalities and

micronucleus in this group (one hour after oral administration) of the blood samples.

Badr et al. [29] observed the radioprotective effect of melatonin when melatonin had been already added to the culture medium of blood lymphocytes and showed that melatonin should be present in the cell at the time of radiation so that it can play its radioprotective role. Kopjar et al. [38] found that peripheral blood lymphocytes treatment with melatonin can be involved in reducing the number of micronuclei after radiation. An in-vitro study conducted by Rostami et al. [37] showed the radioprotective effect of melatonin when the lymphocytes had been treated with melatonin. It should be noted that the highest radioprotective effect on blood lymphocytes was observed in their study one hour after adding melatonin. Similarly, in this study, the effect of melatonin was investigated one hour after oral administration.

These findings may suggest that melatonin might be able to act effectively as a radioprotector. Two hypotheses can be involved in the radioprotective effect of melatonin;

Melatonin may "directly" prevent chromosome damage by collecting free radicals caused by ionizing radiations before they damage the genetic material. Thus, the expansion of the initial damages in the cellular DNA may be significantly reduced.

Melatonin can "indirectly" change the rate of final chromosome damage by activating oxidative repair enzymes. As a result, the damaged DNA in irradiated cells of patients who have already received melatonin would be restored. Also, melatonin may indirectly stimulate the intracellular signals for genes involved in the synthesis of proteins participating in DNA restoration [9].

The literature published about the effects of melatonin suggests that both proposed hypotheses may be correct [39]. The small size and high lipophilicity of melatonin make it possible for this molecule to pass all biological membranes and enter any cell and even into the cellular compartments [12]. Melatonin is widely distributed within cells with the highest concentration at the nucleus [40]. Melatonin tendency for dispersion and accumulation in the nucleus as well as its ability to collect free radicals can be a direct and effective medium for in situ conservation in cells against damages induced by ionizing radiations [26].

Another feature, which probably increases the efficiency of melatonin in reducing oxidative stress is related to its second and third produced metabolites appearing to be efficient scavengers [41]. Some studies have shown an anti-tumor effect for melatonin as it slows down the cell cycle [42].

Conclusions

This study showed that the percentage of those people in the placebo group who had been treated with iodine-131 with no favorable response to treatment (having hyperthyroidism after 6 months of treatment with iodine-131) was higher than the melatonin group. In other words, treatment success in the group receiving the melatonin was higher than control. However, any conclusion about this observation requires further investigation with a larger population and a more precise measurement of the melatonin levels in serum at each stage of sampling.

As a general conclusion, this was the first study examining human in-vivo assessment on the radioprotective effects of melatonin, and melatonin has a positive but not significant effect on reducing the rate of MN. Nevertheless, after 6 month follow-up, the treatment success was higher in the group which received Melatonin. However, future studies with a more extensive study population, longer follow-up (6 months), use of different melatonin doses, and utilizing further biochemical, cytogenetic methods will be recommended.

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Compliance with ethical standards

The Authors declare compliance of the study with all ethical standards. Iranian Registry of Clinical Trials (IRCT); registry No.: IRCT2014090419045N1.

Conflict of interest

There is no conflict of interest.

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