Original

Assessment of Adaptive Response of Gamma Radiation in the Operating Room Personnel Exposed to Anesthetic Gases by Measuring the Relative Gene Expression Changes Ku80, Ligase1 and P53

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ABSTRACT

Background: Some operating room personnel are occupationally exposed to genotoxic agents such as anesthetic gases and ionizing radiation. Adaptive response, as a defense mechanism, will occur when cells become exposed to a low dose of factors harming DNA (priming dose), which in the subsequent exposure to higher dose of those factors (challenging dose), show more resistance and sensibility.

Objective: The aim of this study was to investigate adaptive response or synergy of ionizing radiation in the operating room personnel exposed to anesthetic gases by evaluation of the relative gene expression changes of effective genes for DNA repair such as Ku80, Ligase1 and P53.

Material and Methods: In this case-control study, 20 operating room personnel and 20 nurses (who were not present in the operating room) as controls were studied. Venous blood samples were drawn from participants. In order to evaluate the adaptive response, a challenging dose of 2Gy gamma radiation was applied to blood samples. Moreover, RNA extraction and cDNA synthesis were performed. Gene expression level was studied by RT-qPCR and compared with the control group.

Results: Ligase1 and P53 expression in the operating room personnel was significantly higher than that of the control group before irradiation ($P<0.001$). Statistically, there was no significant difference in the Ku80 and P53 expression in the operating room personnel before and after irradiation.

Conclusion: Given the findings of this study, exposure to challenging dose of gamma radiation can induce adaptive response in expression of Ku80 and P53 genes in operating room personnel.

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Keywords

Adaptive Response; Ionizing Radiation; Anesthetic Gases; Operating Room Personnel; Occupational Exposure; DNA Repair; Gene Expression; RT-qPCR

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Introduction

Some operating room personnel (for example, in the orthopedic, urology, and cardiac angiography operating rooms) are occupationally exposed to genotoxic agents such as anesthetic gases and ionizing radiation [1-3]. Although ventilation and scavenging systems

that mainly reduce the concentration of anesthetic gases are widely used, the complete removal of these gases is next to impossible [3]. Studies have shown that long-term exposure to anesthetic gases can lead to increased oxidative stress, DNA damage, genotoxicity and carcinogenesis [3,4]. Additionally, operating room personnel are exposed to ionizing radiation during cardiothoracic, neuro-spine, orology and orthopedic surgeries. The number of these procedures has increased significantly in the last decade [4]. Occupational exposure of individuals to ionizing radiation in the operating rooms is a serious concern for the safety of personnel and patients. The adverse biological effects of ionizing radiation vary based on the duration of exposure, which generally increases the risk of cancer [5]. Invasive cardiologists are the most exposed to ionizing radiation among health professionals and subsequently lead to an increase in the rate of their somatic DNA damage [6]. Adaptive response, as a defense mechanism in living organisms, occurs when cells are exposed to low dose of a physical or chemical genotoxic agent (priming dose), which in the subsequent exposure to higher dose of the same or another genotoxic agent (challenging dose), show more resistance and less sensitivity; hence, the level of cell damage will be reduced [7]. The low levels of cell damage can trigger signaling pathways that activate the mechanisms of DNA repair. These changes reduce the level of damage caused by high doses of genotoxic agents such as ionizing radiation [8]. Adaptive response has been demonstrated in a variety of in vitro and in vivo systems with end points such as cell survival ratio, gene expression variations, chromosomal aberrations, DNA single and double-strand breaks, carcinogenesis, enzymatic and antioxidant changes, micronucleus induction, and biochemical tests [8-10]. The factors proposed to describe the mechanisms of induction of adaptive response include activating DNA repair mechanisms, inducing the synthesis of new proteins, producing antioxidant compounds, effective detoxification of free radicals, enhancing the immune system, and inducing apoptosis [8]. However, this phenomenon is variable. Sometimes, the damage will be reduced after the challenging dose, or it will have a synergistic or additive effects [11]. Adaptive response variations depend on the type of genotoxic agents, dose and dose rates, cell line, experimental design conditions, time interval between priming and challenging doses, cell cycle stage, P53 status, physiological status and genetic structure of the blood donor [12-13]. One of the biomarkers of adaptive response is gene expression changes; hence, the aim of our study was to investigate adaptive or synergistic effect of ionizing radiation in the operating room personnel exposed to anesthetic gases by evaluating the relative expression changes of effective genes in DNA repair, such as Ku80, DNA Ligase1(Lig1) and P53. Moreover, determining a suitable biomarker for adaptive response was studied. These genes were selected based on recent adaptive response studies [11,14,15]. In this study, we considered chronic doses of anesthetic gases as priming dose, that operating room personnel are exposed as occupational exposure during their professional work, and in order to evaluate the adaptive response, a challenging dose of 2Gy gamma radiation for groups was used.

Material and Methods

Study population and sampling

In this case-control study, the exposed group consisted of 20 personnel working in Shiraz Shahid Beheshti Hospital's operating room (physician, nurse, technician), including 12 men and 8 women aged between 27 and 51 years with the mean age of 34.35± 7.33 years. These individuals had a history of exposure to anesthetic gases, such as N_2O, Isoflurane, and Sevoflurane for at least 3 years and worked in the operating room for at least 6-h per day. The control group consisted of 20 nurses work-

ing in other wards of the hospital, including 12 men and 8 women aged between 25 and 48 years with the mean age of 34.05 ± 6.50 years, who had no occupational exposure to anesthetic gases and ionizing radiation. Demographic data, work experience, alcohol consumption, smoking, medical and genetic history, and history of exposure to chemicals and ionizing radiation were collected through standard questionnaires. The test and control groups were matched for age, gender, lifestyle and smoking habits. If the personnel were recently exposed to ionizing radiation and had any previous or current exposure to other chemical pollutants with genotoxic effects, chronic diseases, alcohol consumption, and smoking habits, they were excluded from the study. About 5 ml of the blood sample was obtained from each donor in EDTA containing vials after obtaining their written informed consent, which was approved by the local Ethics Committee of Shiraz University of Medical Sciences. Each whole blood sample was divided into two equal parts, one was kept as control and the second was exposed to challenging dose of 2Gy gamma radiation.

Irradiation

For adaptive response experiment, blood samples were irradiated at room temperature with a dose of 2Gy gamma radiation as a challenging dose at dose rate of 70 cGy/min (SSD: 50cm) using ^{60}CO gamma-ray source in radiotherapy department of Namazi Hospital, Shiraz, Iran.

RNA Extraction and cDNA Synthesis

Thirty minutes after irradiation, from the irradiated and non-irradiated blood samples total RNA was extracted by the RNX-PLUS Kit (Sina Clon, Iran) according to the kit protocols and quantified using spectrophotometer (HELMA, USA). RNA integrity was confirmed by a 2% agarose gel electrophoresis. cDNA synthesis was done, using RevertAid first Strand cDNA synthesis kit (Takara, Japan) based on the manufacture's protocol.

Real-Time Quantitative polymerase chain reaction (RT-qPCR)

The RT-qPCR reaction was designed after determining the concentration of cDNA, using the designed primers. Primers were designed using the Allele ID7 software (Premier Biosoft International, Palo Alto, USA). To eliminate genomic DNA contamination, the primer design was performed in the exon regions and synthesized by Bioneer Corporation (South Korea), which is shown in Table 1. The β-actin gene was used as the endogenous reference. The mRNA expression was quantitated for Lig1, Ku80, and P53 genes through

Table 1: Primer sequences used for RT-qPCR

Primer Name	Sequence (5´–3´)	Product size (bp)
Ku80 PR-1(forward)	CGACAGGTGTTTGCTGAGAA	223
Ku80 PR-2 (reverse)	TCACATCCATGCTCACGATT	
P53 PR-1(forward)	TGGCCATCTACAAGCAGTCA	212
P53 PR-2 (reverse)	GGTACAGTCAGAGCCAACCT	
Lig1 PR-1(forward)	AGATCCAGCCATTCCAAGTG	194
Lig1 PR-2 (reverse)	GAAGACAAACTCGCCCTCTG	
β – actin PR-1 (forward)	GGGAAATCGTGCGTGACATTAAGG	183
β – actin PR-2 (reverse)	GGAAGGAAGGCTGGAAGAGTGC	

real-time quantitative polymerase chain reaction (RT-qPCR) (Applied Biosystems ™, ABI, USA). Each RT-qPCR reaction was performed in a total volume of 20µL containing 2x SYBR Green qPCR Master Mix (Yekta Tajhiz Azma, Iran) (10µL), primers (2µL-10µmol), deionized water (6µL), and cDNA (2µL). The cycling conditions were as follows: 2 minutes at 95°C (Activation) and 45 cycles (15 s at 95°C (Denaturation), 1 minute at 62°C (Annealing), 1 minute at 72°C (Extension), and 15 s At 95°C (Final Extension). In order to optimize the reaction, using different dilutions of the PCR product, standard charts and reaction efficiency for Lig1 (82%), Ku80 (98%), P53 (95%) and β-actin (82%) were obtained. The results were analyzed using ($R = 2^{-\Delta\Delta Ct}$) and the reference gene β-actin for normalization. Thus, for the completely studied population, the relative expression of Lig1, Ku80, and P53 was obtained. Table 1 shows primer sequences used for RT-qPCR.

Verification polymerase chain reaction and primer design

To verify Lig1, KU80, P53 and β-actin primers with 194, 223, 212 and 183 base pair (bp) band lengths, PCR was performed with a cDNA sample. 5µL of PCR product was loaded on 2% agarose gel. The distinctly mentioned band lengths of each gene were visible after DNA Safe Staining (Sina Clon, Iran) (Figure 1).

Statistical analysis

Statistical analysis was performed using SPSS software version 21. The level of significance was set at $P < 0.05$. Data are represented as mean ± SD. The paired t-test was used to compare the mean of gene expression changes in each group before and after irradiation. Regarding the normal distribution of data by the Kolmogorov–Smirnov test, one-way ANOVA with post-hoc Tukey Test was used to compare the mean of gene expression amongst groups

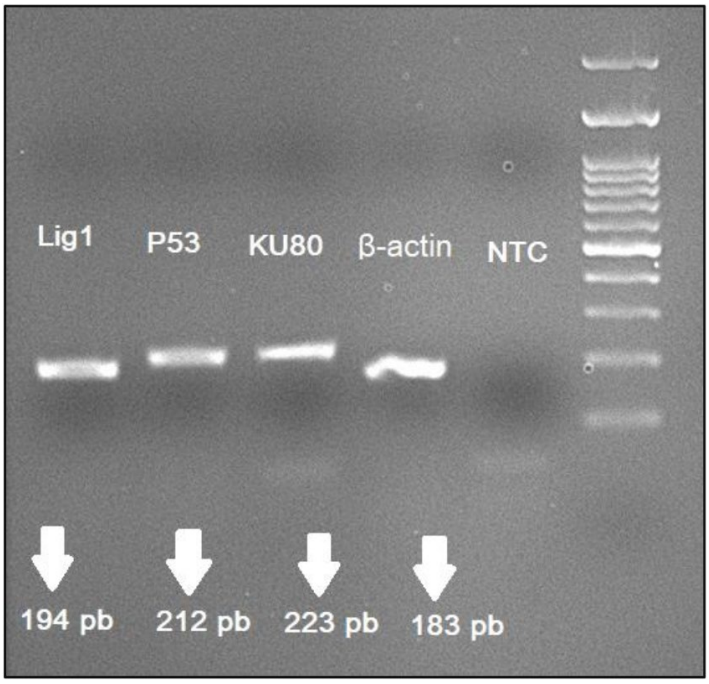

Figure 1: Electrophoresis image of the designed Lig1, P53, KU80 and β-actin primers (194, 212, 223 and 183 bp) which visible in the image.

(operating room personnel and control group in before and after irradiation).

Results

In this study, adaptive response study was performed using gene expression changes in 40 individuals (operating room personnel and control group) after 30 min of challenging dose administration.

The demographic characteristics of the studied subjects are presented in Table 2. There were no significant differences between the groups as far as demographic variables were concerned. None of the participants in both groups was smokers.

In the present study, the control group and operating room personnel were divided into two groups before and after irradiation, based on the challenging dose of ionizing radiation and mean gene expression values for groups are shown in Figures 2, 3 and 4. (Control, Control (+IR), ORP, ORP (+IR)).

The expression of Lig1 in the operating room personnel had a significant increase in

Table 2: Data for control group and Operating room personnel obtained from the questionnaire

Groups	Sample size	Age (years) Mean ± SD	Gender (M or F)	Employ in year Mean± SD	Smoking	Radiation or anesthetic gases exposure
Control	20	34.05 ± 6.50	12(M) 8(F)	10.39± 6.31	No	No
Operating room personnel	20	34.35± 7.33	12(M) 8(F)	9.45± 6.85	No	Anesthetic gases

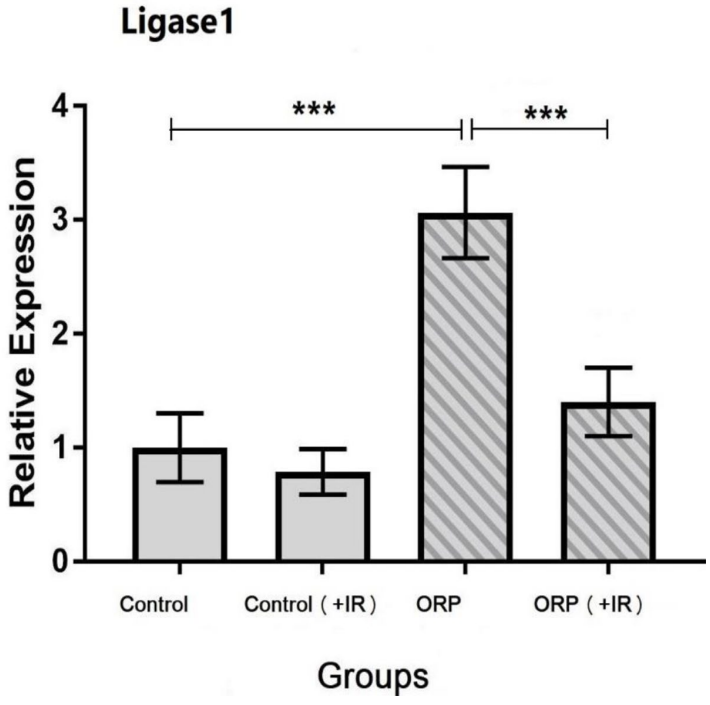

Figure 2: Comparing the relative expression of Lig1 in the control group vs. operating room personnel (ORP) in before and after irradiation. IR: ionizing radiation (2Gy) (*** P<0.001).

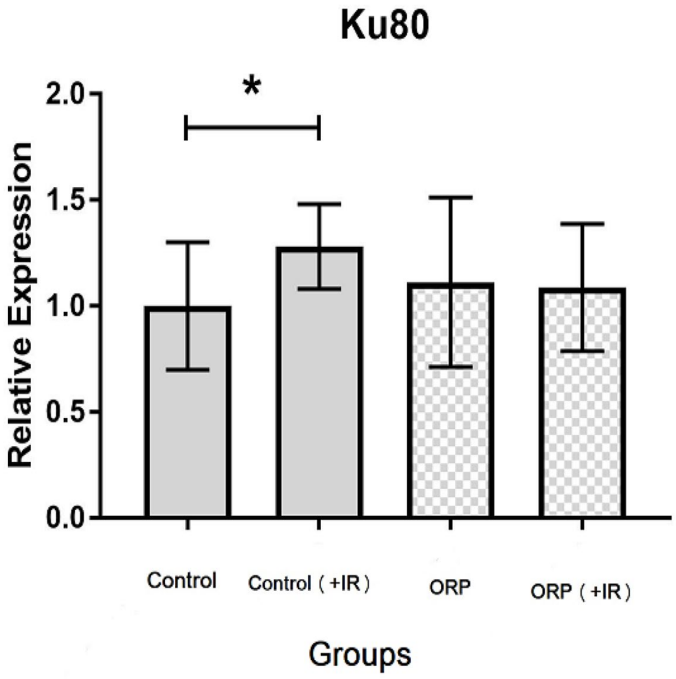

Figure 3: Comparing the relative expression of Ku80 in the control group vs. operating room personnel in before and after irradiation (*P<0.05).

comparison with the before irradiation control group (P<0.001) (Figure 2). However, no significant decrease in the expression of Lig1 was seen after irradiation in the control group (P>0.05). In contrast, Lig1 expression significantly decreased in the operating room personnel after irradiation (P<0.001).

The expression of Ku80 in the control group after irradiation was significantly higher than before radiation (P<0.05) (Figure 3). However, there was no significant difference in the Ku80 expression in the operating room personnel in before and after irradiation (P>0.05).

The expression P53 in the control group after irradiation showed a significant difference compared to the before irradiation (P<0.001) (Figure 4). Moreover, the comparison of P53 expression in the operating room personnel showed a significant difference compared to the control group in before irradiation (P<0.001). However, there was no significant change in the expression of P53 in the operating room personnel in before and after irradiation (P>0.05).

Discussion

The present study aims to assess the adaptive response of gamma radiation in the operating room personnel exposed to anesthetic gases by measuring the relative gene expression changes Ku80, Ligase1 and P53.

A recent study in the target hospital of our study, the mean concentration of anesthetic gases is reported exceeding the global standard (NIOSH) in operating room staff. Moreover, the micronucleus (MN) induction and chromosomal abnormalities in these staff are reported with significant increase compared to the control group. This matter can be a result of extensive application of anesthetic gases, undesirable ventilation and scavenging systems, leakage of anesthetic devices and patients' mask, and high flow rate of anesthetic gases in the operating room [16].

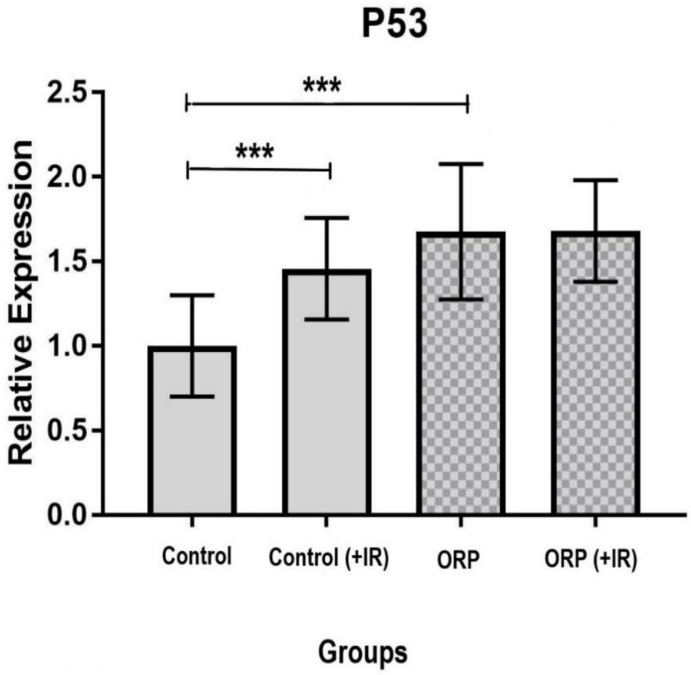

Figure 4: Comparing the relative expression of P53 in control group vs. operating room personnel in before and after irradiation (***P<0.001).

In the present study, Lig1 expression in the operating room personnel in before irradiation had significantly increased compared to the control group. This could be explained by the fact that due to exposure to anesthetic gases and the genetic damages caused by it, the Lig1 plays an active role in repairing the damaged DNA, thereby it has a higher expression. After irradiation, Lig1 expression had significantly decreased in the operating room personnel and showed a high sensitivity to ionizing radiation. Lig1 has an important role in nucleotide excision repair (NER) pathway and the long base excision repair pathway (BER). Therefore, decrease in Lig1 activity contributes to genome instability and carcinogenesis [17]. In accordance with the present results, previous studies have shown the significant upregulation of the Lig1 in human lymphocytes, using the priming dose of 0.1Gy followed by a challenging dose of 2Gy after 4h [11]. Additionally, the upregulation of Lig1 in human primary fibroblasts was observed within 24h after exposure to UV-C radiation [18]. In the present study, the expression of Ku80 in the control group following irradiation significantly increased. Some studies have shown the upregulation of Ku80 expression in human lymphocytes after exposure to priming dose of 0.1Gy and challenging dose of 2Gy after 4h [15]. DSBs is the most important DNA damage that seriously threatens the protection of genetic and epigenetic information. DSBs in human cells is restored through two important pathways namely homologous recombination (HR) and the path of non-homologous end joining (NHEJ). In the G0/G1 phase of the cell cycle, NHEJ is preferred as the principal route in restoring DSBs in human cells. The Ku Heterodimer, as a large protein required for the NHEJ pathway in mammalian cells, consists of Ku70 and Ku80 [15]. DSBs repair is reported as the key mechanistic approach in adaptive response [19].

In the present study, Ku80 and P53 expression in the operating room personnel did not change significantly before and after irradiation. It seems that exposure to anesthetic gases has caused adaptive effects in this group; hence, no significant changes were observed following 2Gy of gamma radiation. Additionally, upregulation of P53 in operating room personnel in comparison with before irradiation control group, could be explained by the fact that due to the presence of DNA damage in the operating room personnel exposed to anesthetic gases, P53 expression increased and suggesting the active role of this gene in repairing these damages. P53 regulates the cell cycle, DNA repair and apoptosis [20]. A significant increase in P53 expression level was observed at priming dose of 0.1, 0.3 and 0.6 followed by 2Gy of challenging dose at 4h and reported an adaptive response at 1 and 5h after the challenging dose [14]. Similarly, in another study, P53 expression in radiation workers was significantly higher than that of the control group and showed that low and chronic doses of ionizing radiation play an important role in increasing the expression of P53 amongst radiation workers [21]. In several studies, the role of P53 in radio-adaptive response was reported [22-24]. Regarding the results of our research and previous studies, P53 expression is important for the safety of workers exposed to genotoxic agents such as ionizing radiation and anesthetic gases. In our study, it seems that P53 expression in the operating room personnel reflects the constant presence of anesthetic gases in the workplace, and the resulting stress to the cell leads to an increased level of P53 for monitoring DNA damage.

The present study may have some limitations. For instance, it is the first that has investigated the radio-adaptive response using gene expression changes in the operating room personnel and there is no similar study in this regard. Therefore, for more investigation of the adaptive response in the operating room personnel, further studies are recommended by evaluating changes in the expression of other genes, different challenging doses, and a different time intervals for examining the gene expression after the challenging dose of ionizing radiation and investigation of other biomarkers such as enzymatic and antioxidant changes and other techniques such as Comet and MN assay. For instance, a cellular adaptive response to chronic exposure to low-dose radiation in interventional cardiologists through significant increasing of three antioxidant and apoptosis factors, was reported following 2Gy in vitro irradiation [6]. Additionally, the radio-adaptive response for radiation workers was studied with a challenge dose of 4Gy of gamma rays by the use of neutral comet assay. Results of this study indicated a significant decrease in DNA damages for the radiation workers compared to the control subjects [19].

One of the limitations of this study is that the type of target or biomarker is of particular importance in examining the radio-adaptive response. In fact, there is a wide range of genes exhibiting different responses to ionizing radiation [25]. However, the genes evaluated in the present study were selected based on the results of recent studies in radio-adaptive response and confirmation of articles [11,14,15].

Conclusion

Given the findings of this study, exposure to the challenging dose of gamma radiation could induce an adaptive response in the expression of Ku80 and P53 genes in the operating room personnel. In addition, these genes can be considered as suitable biomarkers in radio-adaptive response studies. However, this does not mean to ignore the rules of radiation protection in the operating rooms. According to recommendations of the International Commission of Radiological Protection (ICRP), the operating room personnel required to use personnel dosimeters such as TLD dosimeter for monitoring of radiation dose and the received dose should not exceed 20 mSv/year.

Moreover, considering the high level of P53 expression and Lig1 in the operating room personnel in before irradiation, it is necessary to pay more attention and make more precise decisions regarding the health status and medical care of these people.

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Conflict of Interest

None

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