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Dexmedetomidine acts as an oxidative damage prophylactic in rats exposed to ionizing radiation ☆

Dilek Kutanis (Assistant Professor)[a,*], Engin Erturk[a], Ahmet Besir[a], Yucel Demirci[b], Selcuk Kayir[c], Ali Akdogan[a], Birgul Vanizor Kural[d], Zumrut Bahat[e], Emine Canyilmaz[e], Hanife Kara[d]

[a]*Karadeniz Technical University, Medical Faculty, Department of Anaesthesiology and Intensive Care, Trabzon, Turkey*
[b]*Giresun University, Medical Faculty, Department of Anaesthesiology and Intensive Care, Giresun, Turkey*
[c]*Hitit University, Corum Education and Research Hospital, Corum, Turkey*
[d]*Karadeniz Technical University, Medical Faculty, Department of Biochemistry, Trabzon, Turkey*
[e]*Karadeniz Technical University, Medical Faculty, Department of Radiation Oncology, Trabzon, Turkey*

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Abstract

Study objective: To investigate the effects of dexmedetomidine on oxidative injury caused by ionizing radiation.

Design: Randomized controlled experimental study.

Setting: Department of radiation oncology and research laboratory of an academic hospital.

Interventions: Twenty-eight rats were randomized to 4 groups (n = 7 per group). Group S rats were administered physiologic serum; group SR rats were administered physiologic serum and 10 Gy external ionizing radiation. Groups D100 and D200 were administered 100 and 200 μg/kg dexmedetomidine intraperitoneally, respectively, 45 minutes before ionizing radiation.

Measurements: Liver, kidney, lung, and thyroid tissue and serum levels of antioxidant enzymes (glutathione peroxidase [GPX], superoxide dismutase, and catalase) and oxidative metabolites (advanced oxidation protein products, malondialdehyde, and nitrate/nitrite, and serum ischemia-modified albumin) were measured 6 hours postprocedure.

Main results: In group SR, IR decreased antioxidant enzyme levels and increased oxidative metabolite levels ($P < .05$). In plasma, antioxidant enzyme levels were higher and oxidative metabolite levels were lower in groups D100 and D200 than in group SR ($P < .01$). In tissues, hepatic and lung GPX levels were higher in groups D100 and D200 than in group SR ($P < .001$). Renal and thyroid GPX levels were higher in D200 than in group SR ($P < .01$). Thyroid superoxide dismutase levels were higher in groups D100 and D200 than in group SR ($P < .01$). Renal, lung, and thyroid catalase levels were higher in group D200 than in group SR ($P < .01$). Hepatic, renal, and lung advanced oxidation protein products and malondialdehyde levels were lower in groups D100 and D200 than in group SR ($P < .01$). Hepatic, renal, and lung nitrate/nitrite levels were lower in group D200 than in group SR ($P < .05$).

☆ We declare that there is no conflict of interest.

* Corresponding author at: Karadeniz Technical University, Faculty of Medicine, Department of Anaesthesiology and Intensive Care, 61080 Trabzon, Turkey. Tel.: +90 462 3775898.
E-mail address: dilekkutanis@gmail.com (D. Kutanis).

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Conclusions: Dexmedetomidine preserves the antioxidant enzyme levels and reduces toxic oxidant metabolites. Therefore, it can provide protection from oxidative injury caused by ionizing radiation.

1. Introduction

People are often exposed to radiation during medical or paramedical procedures. Ionizing radiation is used for surgery, angiography, and several imaging protocols. It is also frequently used as a cancer treatment. However, these procedures can produce unwanted adverse effects. The basic mechanism of action for ionizing radiation is DNA damage that induces cell death [1]. Ionizing radiation creates reactive oxygen species (ROSs) through water ionization and subsequent reactions with chemicals in the immediate cellular environment. ROSs react with membrane lipids, proteins, and DNA, which is lethal to cells [2,3]. In addition, ROSs negatively impact antioxidant defense mechanisms in cells by reducing the activity of antioxidant enzymes, especially glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase (CAT) [3,4]. Moreover, some destructive oxidative species, such as advanced oxidation protein products (AOPP), malondialdehyde (MDA), nitrite/nitrate (N/N), and ischemia-modified albumin (IMA), are produced during ionizing radiation reactions. Several recent studies have investigated methods to minimize oxidative damage [2] induced by ionizing radiation [2,5-8]. Reducing the amount of ionizing radiation the patient is exposed to is one method of minimizing damage; however, this technique is not a viable damage-reduction method for cancer radiotherapy due to negative effects on tumor response. Antioxidant drugs are another damage-reduction method because they inhibit ROS formation or inactivate ROSs after ionization has occurred.

Anesthetics [9] and anesthesia methods are frequently used during procedures involving radiation, such as radiotherapy [10], invasive imaging applications, or surgery under anesthesia [11]. Several urologic and orthopedic surgical procedures and invasive interventional procedures are performed with radiation imaging. Sedoanalgesia, which combines sedation and analgesia, is commonly used for these types of procedures [11]. For example, sedoanalgesia is frequently used when implanting catheters for high-dose radiation brachytherapy [12]. Dexmedetomidine, an α_2 adrenergic receptor agonist, has sedative, anxiolytic, and analgesic effects. Thus, it is ideal for sedoanalgesia procedures [10]. Dexmedetomidine has been shown to have antioxidant properties in experimental studies [13], and 1 study showed that dexmedetomidine enhanced the SOD activity of human blood [14].

In this randomized prospective study, we investigated the effects of dexmedetomidine on ionizing radiation damage. To this end, we measured the plasma and tissue levels of GPX, SOD, CAT, AOPP, MDA, N/N, and IMA in rats treated with dexmedetomidine before exposure to ionizing radiation.

2. Materials and methods

2.1. Animals and groups

All methods were approved by the Ethical Committee of Laboratory Animal Research of Karadeniz Technical University (protocol no. 4-2013). Ten- to 12-week-old Sprague-Dawley male rats weighing 250-300 g were used in this study. The rats were divided into 4 groups. Group S was administered physiologic serum and were not irradiated (n = 7). Group SR was administered physiologic serum and radiation (n = 7). Group D100 was administered 100 μg/kg dexmedetomidine and radiation (n = 7). Group D200 was administered 200 μg/kg dexmedetomidine and radiation (n = 7). Rats were housed in transparent polycarbonate cages, maintained on a 12-hour light-dark cycle, and kept at 20°C-22°C ± 2°C with 45%-65% humidity. Rats were fed ad libitum with standard food and fresh tap water.

2.2. Anesthesia and radiation

Rats were initially anesthetized by injecting 10 mg/kg xylazine hydrochloride (Rompun 23, 32 mg/mL, Bayer) and 50 mg/kg ketamine (Ketalar 50 mg/mL, Pfizer) intraperitoneally (IP) before irradiation and blood and tissue extraction. For groups S and SR, physiologic serum was injected IP. For groups D100 and D200, 100 and 200 μg/kg dexmedetomidine (Precedex 100 μg/mL, Abbott Park, IL), respectively, was injected IP. At 45 minutes postinjection, all rats were transported in metal-free polycarbonate cages to the Radiotherapy Department at Karadeniz Technical University. Groups SR, D100, and D200 were removed from their cages and exposed to 10 Gy of external ionizing radiation using a cobalt-60 teletherapy machine (80-cm fixed source to surface distance, 2.5-cm depth). Group S underwent a sham irradiation where the rats went through the same handling steps as the other groups but were not irradiated. After the procedure, rats were returned to their cages.

2.3. Plasma and tissue extraction

At 6-hours postprocedure, all rats were sacrificed using cardiac puncture blood collection. Blood was collected and stored in tubes containing no anticoagulant. Subsequently, plasma was collected after centrifugation at 1800*g* for 10 minutes. Aliquots of plasma were prepared and stored in Eppendorf tubes at −80°C for downstream tests. Liver, right kidney, right lung, and thyroid tissue samples were extracted and stored in Eppendorf tubes at −80°C for downstream tests.