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Investigation of the effects of Sugammadex and Rocuronium on rat lung tissue

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Abstract

In this study, sugammadex of used to reverse rocuronium used for surgical operations aimed to be examined effects on the lungs that expel anesthetic agents from the body. The possible mechanism of oxidative damage and the effects of sugammadex on lung morphology are still not understood. Four groups were formed from 32 adult Sprague-Dawley male rats as pure control, control group, sugammadex, and sugammadex-rocuronium. After drug administration, lung tissues were assessed histopathologically and biochemically for oxidative damage. A statistically significant difference was observed between the groups regarding glutathione (GSH) levels in the rat lung. It was observed that rocuronium increased the malondialdehyde (MDA) value, which is considered an indicator of free radical damage in tissues. The sugammadex-rocuronium complex can cause oxidative stress in lung tissue. In group sugammadex, dense fibrosis and lymphoid tissue were found in the connective tissue, while group sugammadex-rocuronium had little fibrosis and lymphoid tissue. In group sugammadex-rocuronium, thickening of the alveolar wall was detected. The effect of sugammadex application on lung tissues has been demonstrated by biochemical and histopathologic data. Rocuronium caused an increase in mast cells in lung tissue. Sugammadex suppressed this increase caused by rocuronium and caused a decrease in mast cells in the lung tissue. Although these data were obtained as a result of experimental studies, we think that they will make a significant contribution to the anesthesia and reanimation patient treatment protocols in the clinic. However, new studies are necessary to determine the toxic effects of sugammadex and sugammadex-rocuronium complex.

Keywords: Sugammadex; rocuronium; lung morphology; oxidative stres; rat

Introduction

Neuromuscular blockade (NMB) is routinely a serious part of general anesthesia [1]. Rocuronium is available for use as a neuromuscular blocking agent that is indicated for routine or rapid intubation in patients under general anesthesia. Non-depolarizing Rocuronium is widely used as a neuromuscular blocker in general anesthesia surgeries. Sugammadex is frequently used as a rocuronium reversal agent [2]. The development of sugammadex and its introduction into clinical practice is a significant advance in the treatment of NMB. Sugammadex is a binder developed specifically as a reversal agent for the aminosteroid NMBs and rocuronium [3, 4]. Sugammadex was developed as a reversal without the limitations of anticholinesterase drugs. It first became known in the scientific community in 2002. Since then, research on this drug has gained momentum through animal and human experiments [5, 6]. It has taken its place among drugs as the first selective relaxant-binding agent based on cyclodextrin. It is known that it has been approved for clinical use in seventy countries around the world in the past years [7]. The sugammadex molecule in the Sugammadex-rocuronium complex is known to repair quickly and safely deep neuromuscular blockade caused by rocuronium binding to plasma [8,]. It is a modified γ-cyclodextrin developed from cyclodextrins used to dissolve steroids. It is a drug that selectively binds to steroidal neuromuscular blockers. This binding encapsulates and inactivates NMBs. The new compound formed is inactive and is removed from the body in accordance with the pharmacokinetic properties of sugammadex [5, 9]. The lungs are an organ that plays a role in the elimination of anesthetic agents from the body [10, 11]. The majority of relevant clinical studies have remained focused on evaluating its effectiveness against NMB [12], because of Sugammadex is specifically produced to reverse the blockade caused by rocuronium [3, 4]. Sugammadex's clinical use has increased due to its rapid and safe recovery. Although many studies emphasize that sugammadex is effective and safe, some studies have revealed potential risks [12]. Since Sugammadex is a relatively new drug [13], its histomorphological effects and oxidative stress mechanism in lung tissue have not yet been revealed. In this study, the possible effects of sugammadex and sugammadex-rocuronium complex on the possible oxidative damage mechanism and lung morphology were investigated.

Materials And Methods

Animals and Study Characteristics

The study was started after approval was received by the Adıyaman University Animal Experiments Local Ethics Committee (Approval number: ADYU-HADYEK: 2019_042). Experiments were performed in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals, and required sensitivity was taken into account.

Rats kept at room temperature of 22-25 °C were fed daily with a standard pellet diet and water ad libitum. The humidity of the room was set to 50-55%. They were subjected to a 12-hour (06.00-18.00) light-dark cycle using cool white fluorescent lamps in order not to disrupt the natural light-dark cycle. 32 adult Sprague-Dawley male rats weighing between 300-350 g were divided into four equal groups by random selection. The groups consisted of the purine group, the control group, the sugammadex group, and the sugammadex-rocuronium group. The purine group was created from animals that did not undergo surgical treatment to obtain baseline values. Rats in our control group were injected intravenously (IV) with 16 mg/kg 0.9% isotonic saline. The Sugammadex group was created by giving 16 mg/kg IV Sugammadex (Bridion®; Schering-Plough Corporation, Oss, Netherlands) to the rats. The group that received 16 mg/kg IV sugammadex injection and three minutes later 1 mg/kg IV rocuronium (Esmeron®; Organon, Istanbul, Turkey) injection was determined as the sugammadex-rocuronium group. All injection procedures were performed through the tail vein. Drug dosage amounts were made according to Bostan et al. [14] and Pühringer et al. studies of [15] references. Three days after the experimental procedures, lung tissue was removed under ketamine/xylazine anesthesia.

Biochemical Procedure

The dissected lung tissue was first washed with physiological saline at +4°C. According to the cold chain principle, the washed tissue was stored in Eppendorf tubes at -70°C until analysis. For MDA and GSH measurements, tissue homogenates were first obtained from tissue samples. Tissue homogenates were created with the help of a cold 0.15 M KCl (10%, w/v) homogenizer. The Uchiyama method was used as a reference for MDA analysis, and studies were carried out using this method [16]. For GSH analysis, Ellman's [17] method was referenced, and applications were made accordingly.

The MDA test, which stands out with the increase in the amount of free oxygen radicals, is an indicator of the presence of oxidative stress. The pink-colored product is made by reading the pink-colored product from the N-butanol phase at 535 and 520 nm due to the reaction with thiobarbituric at 95°C.

Table 1. *Lung biochemical parameters in all groups (n=8)*

Parameter	Purine Control	Control	Sugammadex	Sugammadex+Rocuronium
GSH (nmol/g)	820.75±84.74	767.15±75.75	960.19±137.94[a,b,c]	724.85±84.72
MDA (nmol/g)	1983.89±281.91	1962.26±246.38	1620.12±271.99[d]	2012.74±829.88

[a]P<0.05 compared to Purine Control P:0,041.

[b]P<0.05 compared to Control P:0,003.

[c]P<0.05 compared to Suggammadex+Rocuronium P :0,001.

[d]P<0.05 compared to Suggammadex+Rocuronium P :0,004.

To create the homegen, lung tissue was homogenized with 10% trichloroacetic acid. The resulting homogenate was centrifuged, and an equal volume of 0.67% thiobutyric acid was added to the resulting supernatant. Incubation was carried out with 90°C boiling water for 15 minutes. Centrifugation was applied to the cooled supernatant. MDA concentrations were studied in lung tissue under 532 nm absorbance, and calculations were made using nmol/g tissue. GSH, which reduces harmful peroxides such as lipids and hydrogen peroxide, is an antioxidant enzyme. This enzyme converts reduced glutathione into oxidized glutathione, which is a marker of oxidative stress. 5,5'-dithiobis-2-nitrobenzoic acid is added into the analysis tubes containing the lung tissue. A reaction occurs between this acid and the sulfhydryl groups contained in glutathione. From this reaction, a yellow-greenish product content occurs. GSH concentration density is determined by measuring the absorbance of this product at 410 nm wavelength with a spectrophotometer. The study data are given in nmol/g.

Histopathological Procedure

The lung tissues of the experimental groups were placed in a 10% formaldehyde solution so that the groups would not be mixed. Fixation was applied for one week. Tissues were cleared of fixation solution by washing under tap water. Paraffin blocks were created adhering to the principle of routine histological tissue monitoring during the paraffin block preparation phase. The paraffin blocks we prepared were divided into sections with a thickness of 7 microns. The obtained paraffin sections were stained with Masson trichrome and toluidine blue dyes. Images obtained through a microscope with a digital camera attachment (Carl Zeiss brand Axiocam ERc5 model) were evaluated histomorphologically.

Statistical Tests

The statistical study was carried out using the Statistical Package for the Social Sciences 22.0 program (SPSS Inc., Chicago, IL, USA). First of all, the normal distribution of the data was evaluated with the single sample Kolmogorov-Smirnov test. A one-way ANOVA test was used because our groups were independent of each other, and the data showed normal distribution. All statistical analyses were considered with a 95% confidence interval and are expressed as mean ± standard deviation (SD). The significance value was taken as $p<0.05$.

Results

Biochemical Evaluation

As a result of statistical measurements of GSH levels in rat lungs, purine 820.75±84.74 nmol/g in the control group, 767.15±75.75 nmol/g in the control group, 960.19±137.94 nmol/g in the sugammadex group, in the sugammadex-rocuronium group 724.85±84.72 nmol/g found as wet tissue. MDA, symbol of free radical damage and lipid peroxidation, in the purine control group, 1983.89±281.91 nmol/g, 1962.26±246.38 nmol/g in the control group, 1620.12±271.99 nmol/g in the sugammadex group and 2012.74±829.88 nmol/g in the sugammadex-rocuronium group found as wet tissue (Table 1).

Histopathological Evaluation

Lung tissue was found to have a normal histomorphological appearance in the images of groups 1 and 2 in the examinations made. No pathological findings were found in the epithelium, lamina propria, muscle, and adventitia layer of the bronchial wall. Alveolar walls and vascular structures were normal (figure 1, 1 a-c, 2 a-c). There was a low

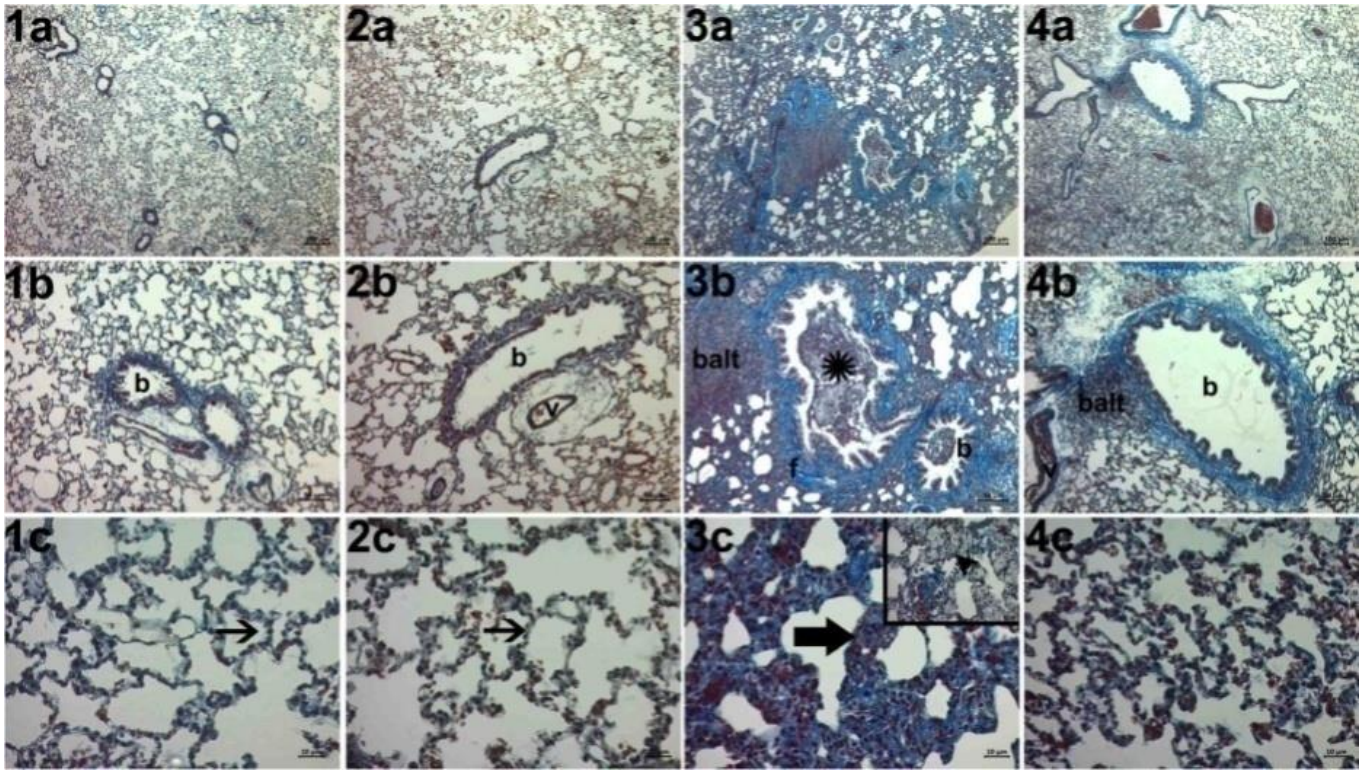

Figure 1. *1a, 1b and 1c; group 1 images of x4-x10-x40 magnifications, respectively; 2a, 2b and 2c; images of x4-x10-x40 magnifications, respectively; 3a, 3b and 3c; group 3 images at x4-x10-x40 magnifications; 4a, 4b and 4c; group 4 images of x4-x10-x40 magnifications (Staining masontrichrome); b; bronchiole, v; blood vessel, f; fibrosis, ax; lymphoid tissue, star; exudate, thin black arrow; normal alveolar wall, thick black arrow; collapse in the alveolar wall, black arrowhead; macrophage cell.*

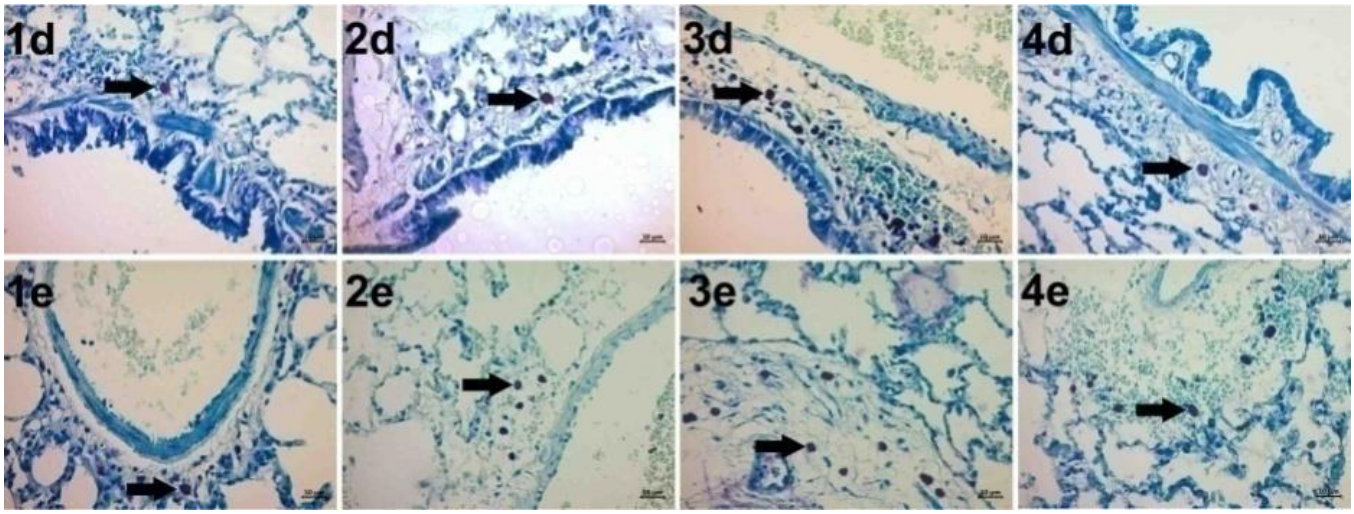

Figure 2. *1d and 1e; images of group 1 at x40 magnification; 2d and 2e; images of group 2 at x40 magnification; 3d and 3e; images of group 3 at x40 magnification; 4d and 4e; images of group 4 at x40 magnification; (Staining toluidine blue); black arrow; mast cells*

density of mast cells around the bronchiole and vessel (figure 2, 1 d,e - 2 d,e). In the examinations of group 3, the epithelium of the bronchiole walls was normal, but there was fibrosis and dense lymphoid tissue in the connective tissue. In addition, findings of exudate were found in the lumen of the bronchiole. There was a collapse in the alveolar wall, dilatation of the alveolar capillaries, and dense macrophage cells (figure 1, 3 a-c). In addition, dense mast cells were seen around the bronchiole and vessel (figure 2, 3 d-e). In the examinations performed in Group 4, the epithelium of the bronchiole walls was normal, and there was little fibrosis and lymphoid tissue in the connective tissue. Thickening of the alveolar wall was detected (figure 1, 4 a-c). In addition, a decrease in the density of mast cells was observed around the bronchiole and vessel (figure 2, 4 d-e).

Discussion

Neuromuscular blocking agents (NMBAs) are important elements of general anesthesia to improve surgical outcomes [18]. There used to be only a reversal agent to revert NMB. This reversal agent had several disadvantages [2, 19]. Sugammadex is a new pharmaceutical agent [13]. It antagonizes steroidal neuromuscular blocking agents such as rocuronium [2, 19]. Sugammadex has also been reported to be safe for reversing NMB [20]. It came into use in December 2015 after receiving clinical use approval from the United States Food and Drug Administration (FDA). However, in preclinical studies, there is no clear information about whether sugammadex application has minor side effects [21]. Additionally, since it is a new drug, more studies are needed in this field [13].

When the case report of sugammadex-resistant rocuronium-induced respiratory paralysis in Marie-Tooth disease is examined, It has been reported that systematic studies are needed to clarify the conditions that place patients at risk of long-term stroke after receiving rocuronium in combination with sugammadex [22]. Therefore, we planned this study considering it was important with this experimental study we have conducted; important information is provided in the literature. Although these data were obtained as a result of experimental studies, we believe that they will make a significant contribution to anesthesia and reanimation patient treatment protocols in the clinic.

Alagöz et al. showed no significant histopathological changes become evident in the group in which they administered sugammadex at a dose of 4 mg/kg; however, when administered at a dose of 16 mg/kg in the group, widespread irregularity of muscle fibers, degeneration, and openings between muscle fibers stated that they found it [23]. We determined the dose of sugammadex in our experimental group as 16 mg/kg based on the information presented to us by Alagöz and his friends in their studies. In addition, the study of Bostan et al. emphasized that rats receiving only rocuronium showed more significant histopathological changes compared to rats receiving only sugammadex. Their explanation is that sugammadex not only has a minimal effect when applied alone but may also worsen rocuronium-induced histopathological degeneration.

The lung is one of the vital organs that ensures the continuity of the vital cycle. If it cannot perform its duty, it is impossible to continue life [24]. General anesthesia is known to have profound effects on lung function. However, it is difficult to generalize the effects of anesthesia on respiratory function [25]. The effect that NBAs can have on the lung tissue, which is such an important organ for vital functions, is very important. An organ that is so important for vital functions how it will affect is very important by NBAs used for anesthetic needs.

Anesthetic agents used during surgical operations can be determinants of oxidative stress. It has been reported that the resulting oxidative stress causes lung damage, is a trigger for many events in the organism and is also associated with various complications in terms of clinical effects [26]. It is known that an increase in oxidative stress causes both damage at the molecular level and disruption of the oxidant-antioxidant balance in the organism [27]. Pathological conditions caused by oxidative stress can cause temporary or permanent damage to tissues [28]. While a high MDA level is defined as one of the markers of oxidative stress [29], the increase in GSH level also indicates the antioxidant defense system against oxidative stress [30]. Therefore, we first studied tissue markers of oxidative stress mainly to test the protective role of Sugammadex. Our study revealed that rocuronium causes lung damage by increasing oxidative stress in the tissue, and Sugammadex plays a protective role by increasing the antioxidant system. Koc et al. reported that Sugammadex inhibits the increase in MDA levels and significantly suppresses the decrease in GSH levels. They said that Sugammadex might be useful in preventing oxidative stress [31].

Mast cells, which play a significant role in the occurrence of pathological processes, are cells located throughout the body, including the respiratory system organs and other organs [32, 33, 34]. It is also known that the lungs of a healthy adult individual contain many mast cells under normal conditions [35, 36]. Researchers have reported that both anaphylaxis due to Sugammadex and allergic reactions to the Sugammadex-

rocuronium complex may occur [37].

Yeşiltaş and his colleagues [38] stated that rocuronium and sugammadex were investigated in experimental studies on the liver and pancreas, but their effects on the lungs were neglected. They also demonstrated that rocuronium-induced allergic effects in rat lungs were alleviated by sugammadex. When they histomorphologically examined the rat lungs of the experimental group in which sugammadex was applied, they stated that there was a slightly thickened alveolar wall in some regions. They explained that the number of mast cells in rat lung tissue was higher in the experimental group to which they applied rocuronium compared to all experimental groups. In our study, we observed that Sugammadex decreased the number of mast cells, and rocuronium increased, as in the study conducted by Yeşiltaş et al. We observed a significant increase in the alveolar wall in the morphological examination of lung tissue after rocuronium application. Increased MDA and decreased GSH levels support the morphological data. Although we see that our study data supports the literature data, we think that more studies are needed. As stated by Yeşiltaş et al., we observed that the research on the histomorphological and biochemical effects of sugammadex and rocuronium complex on the lung in the literature is still limited and insufficient.

In 2021, Yeşiltaş et al. [38] reported that the effects of rocuronium and sugammadex on the lungs were neglected, and there were not enough studies. As a result of our literature searches, no study has been found on the lungs in this field since 2021. We see that work restrictions still continue. We underline that more studies are needed in this field, as emphasized by Yeşiltaş et al [38].

Conclusion

Sugammadex and sugammadex-rocuronium complex were determined by histomorphological and biochemical effects on rat lung tissue after NMB. It was concluded that the sugammadex application did not have a negative effect on lung tissues. Additionally, sugammadex can suppress rocuronium-induced anaphylaxis and allergy by reducing the number of mast cells in the lung tissue. It was found that rocuronium did not cause pathological consequences in lung tissue morphology but caused oxidative damage through GSH and MDA. Although our study results are first, new studies will be more effective in revealing the possible effects of sugammadex and sugammadex-rocuronium complex on lung tissue. Finally, we can say that this study, like all research, is limited. These limitations are due to the lack of similar studies in the literature. Including new studies in the literature and increasing the number of studies will benefit future studies. Another limitation of our study results is that we need clinical data. It is impossible to say whether it correlates with clinical findings based on experimental study data. However, it is possible to say that it is a preliminary study for future research and contains important data.

Ethical Declarations

Adıyaman University Animal Experiments Local Ethics Committee (Approval number: ADYU-HADYEK: 2019_042).

Conflict of Interest Statement

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financial Disclosure

No financial support was received for the study.

Data availability statement

The authors confirm that the data supporting the findings of this study are available in the article.

Author Contributions

All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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