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The experimental study of dexamethasone effectiveness in a model of lipopolysaccharide-induced acute lung injury in rats

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ABSTRACT

Aim. To evaluate the efficacy and safety of dexamethasone at various doses in an experimental model of direct acute lung injury (ALI).

Materials and methods. The study was performed on 80 white outbred male rats, in which ALI was modeled by intratracheal administration of lipopolysaccharide. The animals were divided into 4 groups: the control group and three experimental groups (groups 1–3), where the animals were intraperitoneally administered dexamethasone at doses of 0.52, 1.71, and 8.00 mg / kg / day, respectively, for 3 days. A complete blood count, blood biochemistry test, and hemostatic tests were performed to assess the efficacy and safety of dexamethasone on day 3 of the experiment The severity of pulmonary edema was assessed by changes in the lung weight coefficient and the wet / dry weight ratio.

Results. The use of dexamethasone in the ALI model increased the survival of rats in groups 1 and 2 by 35% ($p < 0.05$), and in group 3 only by 20% compared with control animals. The rat lung weight coefficient and the wet / dry weight ratio when using dexamethasone at all doses studied were equally reduced by an average of 28% ($p < 0.05$) and 17% ($p < 0.05$), respectively ($p < 0.05$). The severity of side effects of dexamethasone (hyperglycemia, hyperproteinemia, hyperkalemia, hypercoagulability, increased activity of creatine phosphokinase in the blood) was dose-dependent and was maximum in group 3 (dexamethasone dose 8.00 mg / kg / day).

Conclusion. The effectiveness of both low (0.52 mg / kg / day) and high (8.00 mg / kg / day) doses of dexamethasone in an experimental model of ALI in rats is characterized by the same anti-edematous effect. Based on the results of the blood tests and the analysis of rat survival, the use of dexamethasone at the lowest dose (0.52 mg / kg / day) should be considered the safest.

Keywords: lipopolysaccharide, dexamethasone, acute lung injury, acute respiratory distress syndrome, biomodeling

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Экспериментальное исследование эффективности дексаметазона на модели липополисахарид-индуцированного острого повреждения легких у крыс

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РЕЗЮМЕ

Цель. Оценить эффективность и безопасность применения дексаметазона в различных дозах на экспериментальной модели прямого острого повреждения легких (ОПЛ).

Материалы и методы. Исследование выполнено на 80 белых беспородных самцах крыс, у которых моделировали ОПЛ посредством интратрахеального введения липополисахарида. Животные были разделены на четыре группы: контрольная группа и экспериментальные группы № 1–3, где животным по лечебной схеме (внутрибрюшинно, 1 раз/сут, в течение 3 сут) вводили дексаметазон в дозах 0,52; 1,71 и 8,00 мг/кг/сут соответственно. В целях оценки эффективности и безопасности дексаметазона на 3-е сут эксперимента проводили клинический, биохимический и гемостазиологический анализ крови, а также оценивали выраженность отека легких по изменению массового коэффициента и степени влагонасыщения органа.

Результаты. Использование дексаметазона в модели ОПЛ повышало выживаемость крыс в сравнении с контрольными животными в группах № 1 и 2 на 35% ($p < 0,05$), а в группе № 3 – только на 20%. Массовый коэффициент легких и степень влагонасыщения легких у крыс при использовании дексаметазона во всех исследованных дозах были одинаково снижены в среднем на 28% ($p < 0,05$) и 17% ($p < 0,05$) соответственно ($p < 0,05$). Степень выраженности побочных эффектов дексаметазона (гипергликемия, гиперпротеинемия, гиперкалиемия, гиперкоагуляция, повышение активности креатинфосфокиназы в крови) носила дозозависимый характер и была максимальной в группе № 3 (доза дексаметазона 8,00 мг/кг/сут).

Заключение. Эффективность как низких (0,52 мг/кг/сут), так и высоких (8,00 мг/кг/сут) доз дексаметазона на экспериментальной модели ОПЛ у крыс характеризуется одинаковым противоэдематозным эффектом. По совокупности результатов лабораторных исследований крови и анализа выживаемости крыс наиболее безопасным следует считать применение дексаметазона в минимальной дозе (0,52 мг/кг/сут).

Ключевые слова: липополисахарид, дексаметазон, острое повреждение легких, острый респираторный дистресс-синдром, биомоделирование

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Over the past two decades, humanity has constantly faced challenges posed by outbreaks of infectious diseases caused by MERS-CoV, SARS-CoV, influenza A/H1N1, and SARS-CoV2. Severe forms of these infectious diseases often lead to significant damage to the lung tissue, up to the development of adult acute respiratory distress syndrome (ARDS) with 35–45% mortality [1].

One of the methods to find the best means of diagnosing, preventing, and treating ARDS in humans is experimental biomodeling of acute lung injury (ALI) in laboratory animals, which is as close as possible to the clinical manifestations of ARDS [2]. The best experimental model of ALI should reproduce the mechanisms and consequences of ARDS in humans and have the following features: clinical (acute onset, diffuse bilateral lung injury, acute exudative phase, proliferation and fibrosis in the end); pathophysiological (ventilation – perfusion mismatch, hypoxemia, decreased lung compliance, impaired alveolar fluid clearance); biochemical (increased concentration of proinflammatory cytokines, hemostatic disorders), and pathomorphological changes (neutrophil infiltration of lung tissue, damage to the alveolar epithelium and impaired permeability of the blood – air barrier, formation of hyaline membranes) [2]. The model of lipopolysaccharide-induced ALI in laboratory animals fully meets the above requirements and is widely used by researchers to search for and justify anti-inflammatory therapy regimens for ARDS using glucocorticoids [3, 4].

For example, M. Qin et al. [5] and J.W. Jang et al. [6] observed inhibition of NF-κB, p38, and NLRP3 inflammasome pathways when dexamethasone was administered at doses of 5 and 6 mg / kg in a model of ALI in mice, which led to a decrease in mortality, pulmonary edema, neutrophil tissue infiltration and microthrombosis in the lung vessels, as well as to a decrease in the levels of proinflammatory cytokines in the blood and bronchoalveolar lavage fluid. Another study using a similar experimental model showed that dexamethasone at a dose of 1 mg / kg exhibited antioxidant effects, inhibiting the functioning of inducible NO synthase in macrophages and polymorphonuclear leukocytes and increasing the expression of heme oxygenase-1 in the lung tissue [7]. Another positive effect of dexamethasone therapy revealed in the experiment was a decrease in the concentration of degradation products of autoantibodies in the peripheral blood flow and bronchoalveolar lavage fluid in mice [8].

In clinical practice, glucocorticoids are used as part of the complex therapy for ARDS, but their role in this therapy is still intensively discussed by the medical community. The results of meta-analyses on the evaluation of the effectiveness of glucocorticoids are often contradictory due to differences in patient selection, heterogeneity of ARDS causes, administration regimens (starting dates, pharmacological agents, dosage, treatment duration), and data processing [3].

The aim of the study was to assess the efficacy and safety of dexamethasone at various doses in an experimental model of direct ALI.

MATERIALS AND METHODS

The experiment was performed on 80 outbred male rats (age: 8–10 weeks, body weight: 310–320 g). The animals were kept in the vivarium in compliance with the basic hygienic requirements: temperature 20–24 °C, 12-hour light / 12-hour dark cycle, free access to food and water. The study was carried out in accordance with the requirements of the Order of the Ministry of Healthcare of Russia No. 199n of 01.04.2016 "On the Approval of the Rules of Good Laboratory Practice".

ALI was modeled by intratracheal (i/t) administration of lipopolysaccharide (LPS) of the *Salmonella enterica* cell wall (Sigma-Aldrich, USA) at a dose of 20 mg / kg. Before i/t administration, the animals were anesthetized with an intraperitoneal (i/p) injection of Zoletil 100 at a dose of 4.0 mg / kg. Intratracheal administration of LPS was performed using the MicroSprayer Aerosolizer device (model IA-1B, USA) 5 min after the animals were anesthetized.

The animals were divided into 4 groups: the control group with ALI and the experimental groups. Three hours after the modeling of ALI according to the treatment regimen (i/p, OD for 3 days), the animals were administered dexamethasone at doses of 0.52; 1.71 and 8.00 mg / kg. Doses of dexamethasone were calculated using the technique of interspecies dose conversion taking into account body surface area and were equivalent to daily doses of glucocorticoid for humans equal to 6 mg, 20 mg, and 94 mg, respectively [9].

Blood samples were taken for examination from the caudal vena cava on day 3 of the experiment. Complete blood count was performed on the automated veterinary hematological analyzer (Mythic 18 Vet, Switzerland), and blood biochemistry test was performed on the automated analyzer (ChemWell 2910, USA). Partial thromboplastin time (PTT), prothrombin time (PT), fibrinogen level, and antithrombin activity (in %) were determined on the semi-automated coagulation analyzer (Tcoag KC 4 Delta, Ireland). The level of soluble fibrin monomer complexes (SFMCs) was studied in the paracoagulation phenanthroline test (NPO Renam, Russia). Blood gas level and electrolyte composition were studied using the i-STAT automatic

analyzer (Abbott, USA). The following parameters of blood gas and electrolyte composition were determined: Na, K, Ca, pH, pCO_2, pO_2, TCO_2, HCO_3, BE, sO_2. After taking blood samples from the animals, the severity of pulmonary edema was assessed by conducting the morphometric analysis with the determination of the lung weight coefficient (LWC) and the wet / dry weight ratio (W / D ratio). LWC was calculated using the formula (lung weight, g / animal weight, g) × 1,000. The W / D ratio was calculated by the formula: wet lung weight, g / dry lung weight g. Before calculating the W / D ratio, the lungs were dried for 5 days in a thermostat at 37 ºC.

To test the hypotheses presented in this study, the statistical analysis of the results was carried out using the Graph Pad Prism 8.0 program. The results were presented as the median and the interquartile range *Me* [Q_1; Q_3]. The Kruskal – Wallis test was used for multiple comparisons of quantitative variables with further post hoc pairwise comparison using the Dunn's test. The relationship between qualitative variables (mortality) was assessed by constructing four-fold contingency tables and performing the Fisher's exact test based on them, followed by constructing a Kaplan – Meier survival curve. The differences were considered statistically significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

Dyspnea and tachypnea were more often observed in rats of the control group than in comparison groups, in which rats were administered dexamethasone at various doses, which indicated the development of respiratory failure. The survival rate in the control group was 60%. The survival rate in groups 1 (dexamethasone at a dose of 0.52 mg / kg / day) and 2 (dexamethasone at a dose of 1.71 mg / kg / day) reached 95%, and in group 3 (dexamethasone at a dose of 8.00 mg / kg / day) was 80% (Fig.1).

In groups 1–3, statistically significant differences were observed in the values of LWC compared with the control group ($p = 0.002$, $p = 0.03$, $p = 0.0001$, respectively). The W /D ratio in the lungs also turned out to be significantly lower in all three experimental groups than in the control group ($p = 0.006$ and $p = 0.04$, $p = 0.02$) (Fig. 2).

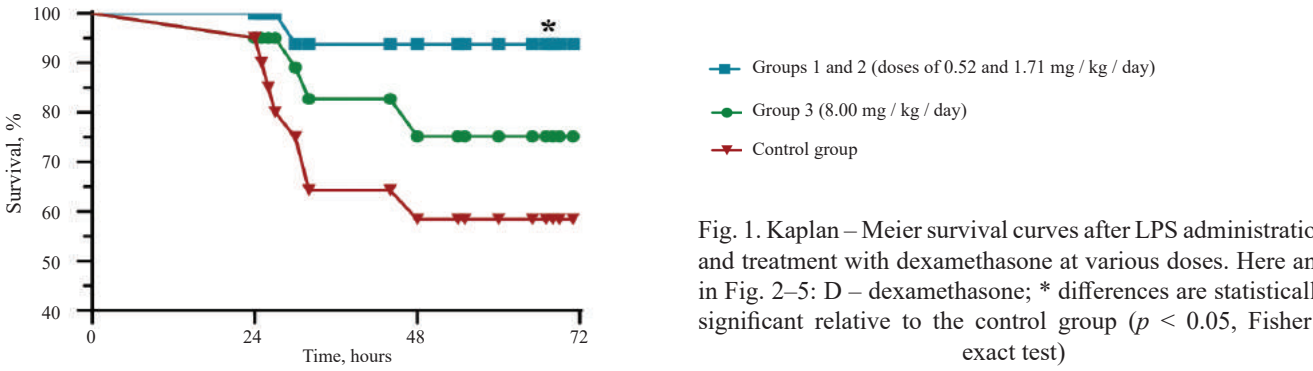

Fig. 1. Kaplan – Meier survival curves after LPS administration and treatment with dexamethasone at various doses. Here and in Fig. 2–5: D – dexamethasone; * differences are statistically significant relative to the control group ($p < 0.05$, Fisher's exact test)

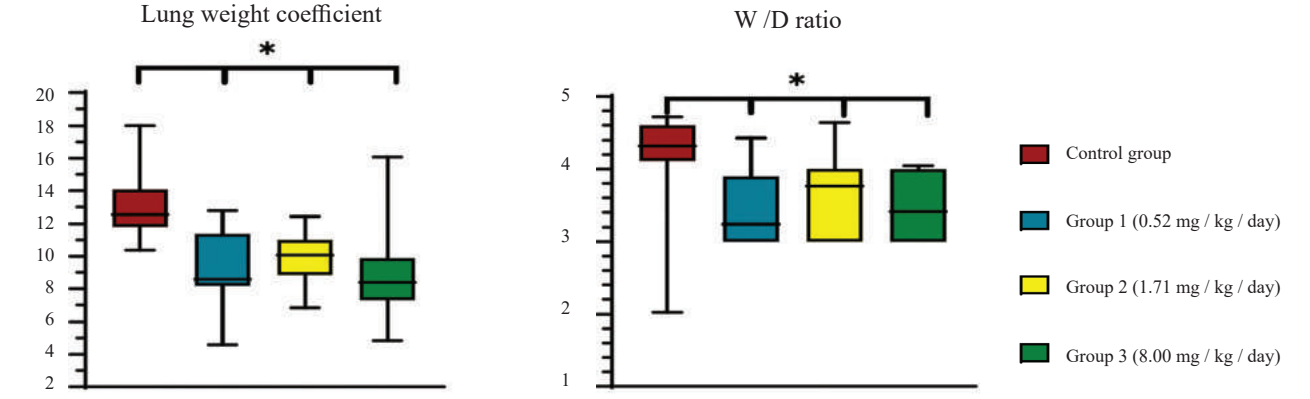

Fig. 2. Lung weight coefficient and the W / D ratio in rats on day 3 after modeling acute lung injury *Me* [Q_1; Q_3]. * differences are statistically significant relative to the control group ($p < 0.05$, Kruskal – Wallis test)

The use of dexamethasone led to typical changes in the leukocyte formula, which manifested by significantly lower absolute and relative lymphocyte count (p = 0.002, p = 0.02, p = 0.04). At the same time, an increase in the absolute and relative monocyte count (p = 0.03, p = 0.007, and p = 0.01, respectively) and granulocyte count (p = 0.08, p = 0.007, p = 0.09) was observed. The number of platelets was significantly smaller in group 3 when compared with groups 1, 2, and the control group (p = 0.006, p = 0.004, p = 0.02) (Table).

When comparing the concentrations of sodium and ionized calcium in the blood of rats in the experimental groups, no significant differences were found, although these groups showed changes depending on the doses of dexamethasone used. Groups 2 and 3 (Fig. 3) had higher potassium levels compared to the

Table

Parameters of complete blood count in rats on day 3 after modeling acute lung injury and treatment with dexamethasone at various doses, *Me* [Q_1; Q_3]

Parameter	Experimental groups			
	control group	group 1 (dexamethasone 0.52 mg /kg/mg)	group 2 (dexamethasone 1.71 mg/kg/mg)	group 3 (dexamethasone 8 mg/kg/mg)
Leukocytes, 10^9 / l	8.6 [7.0; 11.0]	7.9 [6.9; 8.0]	8.3 [6.7; 11.0]	8.5 [7.2; 10.0]
Lymphocytes,10^9 / l	5.4 [4.6; 5.8]	1.7* [0.8; 2.2]	2.1* [1.4; 2.8]	2.4* [1.6; 3.0]
Monocytes, 10^9 / l	0.4 [0.3; 0.5]	0.9* [0.7; 1.2]	1.0* [0.7; 1.3]	1.0* [1.0; 1.3]
Granulocytes, 10^9 / l	1.5 [1.3; 1.7]	4.4* [3.3; 5.0]	4.6* [3.6; 6.0]	4.1* [3.7; 4.5]
Lymphocytes, %	74.0 [73; 75]	19.0* [17.0; 23.0]	25.0* [20.0; 30.0]	31.0* [30.0; 34.0]
Monocytes, %	5.0 [5.0; 6.0]	14.0* [10.0; 15.0]	13.0* [11.0; 15.0]	15.0* [13.0; 16.0]
Granulocytes, %	21.0 [20.0; 21.0]	67.0* [55.0; 74.0]	62.0* [57.0; 68.0]	54.0* [50.0; 57.0]
Erythrocytes 10^{12} / l	7.5 [7.4; 7.7]	6.9 [6.5; 7.8]	7.5 [7.2; 8.1]	7.7 [7.3; 7.9]
Hemoglobin, g / l	154.0 [150.0; 160.0]	156.0 [147.0; 166.0]	153.0 [147.0; 166.0]	163.0 [155.0; 164.0]
Platelets, 10^9 / l	519.0# [515.0; 592.0]	548.0# [506.0; 598.0]	511.0# [443.0; 586.0]	410.0 [335.0; 449.0]

Differences are statistically significant: * relative to the control group (p < 0.05, the Kruskal – Wallis test); # relative to group 3 (p < 0.05, the Kruskal – Wallis test).

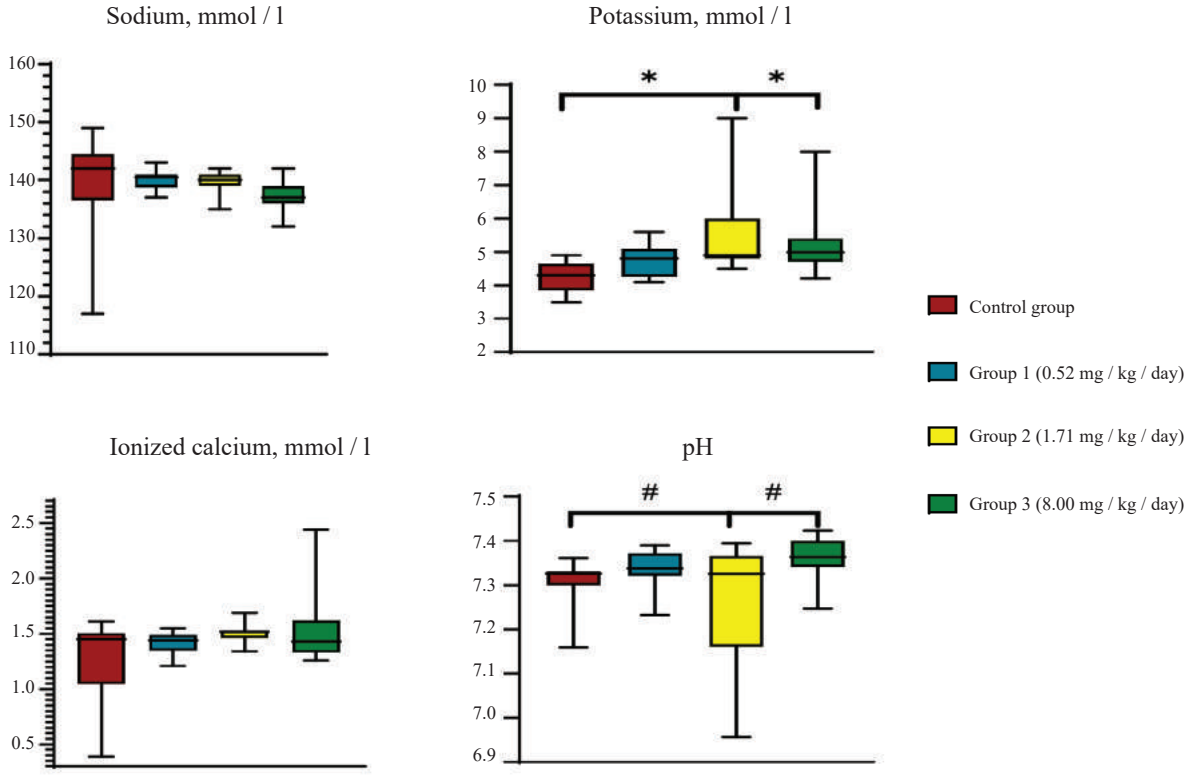

Fig. 3. The concentration of sodium, potassium, ionized calcium, and the pH level in the blood on day 3 after modeling acute lung injury and treatment with dexamethasone at various doses, *Me* [Q_1; Q_3]). * differences are statistically significant relative to the control group (p < 0.05, the Kruskal – Wallis test)

control group ($p = 0.002$, $p = 0.004$). The pH values were significantly higher in group 3 compared to the control group and group 2 ($p = 0.02$, $p = 0.04$) There were no significant differences among the groups when comparing pCO_2, pO_2, TCO_2, HCO_3, BE, sO_2 in venous blood.

Compared with the values in the control group, the concentration of glucose in the blood of experimental animals was significantly higher ($p = 0.01$, $p = 0.0009$, and $p = 0.0002$ for groups 1, 2, and 3, respectively), and the dose of dexamethasone determined how much the parameter increased. When analyzing the content of total protein, its concentration in animals of group 3 was significantly higher than in the control group ($p = 0.01$), while the level of albumin was increased in all experimental groups ($p = 0.02$, $p < 0.0001$, $p = 0.005$ for groups 1, 2, and 3, respectively). Activity of CPK was significantly higher in animals treated with dexamethasone at doses of 1.71 and 8.00 mg / kg / day (groups 2 and 3) compared to the control group ($p = 0.006$, $p = 0.02$, respectively) (Fig. 4).

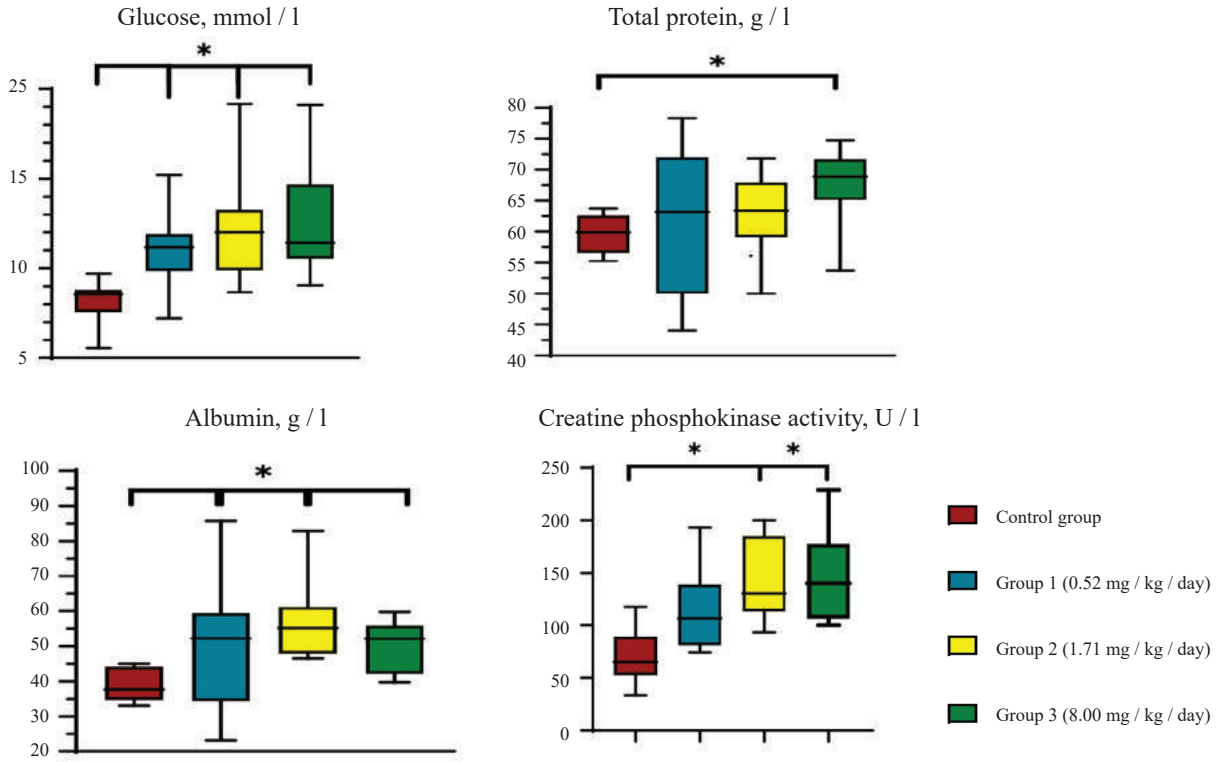

Fig. 4. Concentration of glucose, total protein, albumin, and creatine phosphokinase activity in blood on day 3 after modeling acute lung injury and treatment with dexamethasone at various doses, *Me* [Q_1; $Q3$]. Differences are statistically significant: * relative to the control group ($p < 0.05$, the Kruskal – Wallis test); # relative to the dexamethasone 8 mg / kg / day group ($p < 0.05$, the Kruskal – Wallis test)

The concentration of SFMCs in blood plasma of the animals in group 3 (dose of dexamethasone 8 mg / kg / day) was significantly higher not only when compared with the control group ($p < 0.0001$), but also when compared with groups 1 and 2 ($p = 0.008$, $p = 0.01$, respectively). Significant differences in PT were observed when comparing groups 2 and 3 with the control group. In these groups, the parameter was significantly lower than in the control group ($p = 0.03$, $p = 0.0009$, respectively). Antithrombin III activity was significantly lower in groups 2 and 3 ($p = 0.003$, $p = 0.0002$) compared to the control group. In addition, antithrombin activity was lower in group 3 compared to group 1 ($p = 0.02$). No significant difference was found in the concentration of fibrinogen when comparing groups 1–3 with the control group (Fig. 5). There were no significant differences between the groups when comparing the PTT values in venous blood.

It was shown that after i/t administration of LPS, the rats developed bilateral diffuse lung damage, leading to edema with high LWC and W /D ratio, as well as to death of 40% of the animals in the group. The obtained data are consistent with the results of previous studies using the selected experimental ALI model [2, 6, 10, 11].

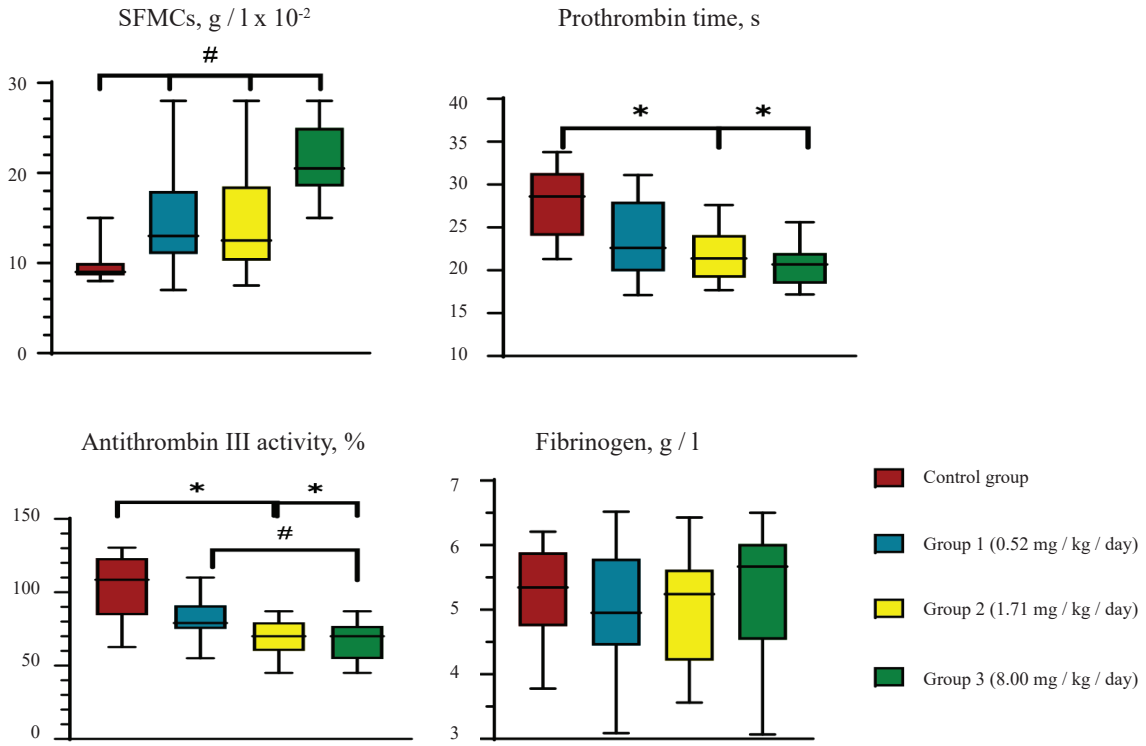

Fig. 5. Coagulation parameters in rats on day 3 after modeling acute lung injury and treatment with dexamethasone at various doses, *Me* [Q_1; Q_3]. Differences are statistically significant: * relative to the control group ($p < 0.05$, the Kruskal – Wallis test); # relative to group 3 ($p < 0.05$, the Kruskal – Wallis test).

The use of dexamethasone in all studied doses led to positive therapeutic effects including a decrease in the volume of lung tissue damage, which was accompanied by correction of respiratory failure (normopnea, normalization of blood pH) and decreased mortality. At the same time, significant dose-dependent side effects of glucocorticoid therapy developed including hyperglycemia, hyperproteinemia, hyperalbuminemia, hyperkalemia, and increased CPK activity in the blood. In addition, coagulation disorders were observed including high values of SFMCs in combination with low PT and low antithrombin III activity, which, in combination with hyperproteinemia, aggravated hypercoagulability that progressed while accompanying inflammation. In rats receiving dexamethasone therapy, the analysis revealed a decreased lymphocyte and platelet count, as well as an increase in the number of granulocytes and monocytes in the blood.

In group 1, where dexamethasone was administered at a dose of 0.52 mg / kg / day, the lowest mortality among all groups and the lowest values of LWC and the W/D ratio were observed. The glucose concentration was higher than in the control group, but was the lowest among all comparison groups. Despite the large number of SFMCs, no significant decrease in PT was observed, and antithrombin III activity was the highest among all groups, which may indicate a balanced state of coagulation and anticoagulation systems, as well as a low risk of thrombotic complications.

In group 2, in which dexamethasone was administered at a dose of 1.71 mg / kg / day, the survival rate was similar to that in group 1. At the same time, when dexamethasone was administered at this dose, the highest values of LWC, W/D ratio, and monocyte count in the blood were observed among all experimental groups in which dexamethasone was used. High concentrations of glucose and potassium in the blood similar to those in group 3 were detected. SFMC parameters were significantly higher, while PT and antithrombin III activity were lower than in the control group.

The highest mortality in animals was observed in group 3 (dexamethasone dose was 8.00 mg / kg / day), despite low values of LWC and W / D ratio. The concentration of glucose, potassium, total protein, albumin, and CPK activity were the highest in this group, and PT was the shortest. The parameters characterizing the blood coagulation system indicated a high risk of thrombosis as the maximum values of

SFMCs, the minimum values of PT, and the minimal activity of antithrombin III were recorded. A low platelet count and severe hypercoagulability might indicate increased platelet consumption.

CONCLUSION

As a result of the study, it was found that the effectiveness of both low (0.52 mg / kg / day) and high (8.00 mg / kg / day) doses of dexamethasone in an experimental model of LPS-induced ALI is characterized by a similar antiedematous effect. Based on the results of blood tests and analysis of animal survival, the use of dexamethasone at the minimum dose (0.52 mg / kg / day) should be considered the safest. Despite significant anti-inflammatory effects on the lung tissue, the administration regimen of dexamethasone at the maximum dose (8.00 mg / kg / day), which is equivalent to pulse therapy, was accompanied by the occurrence of the most pronounced adverse events, namely: hyperglycemia, hyperproteinemia, hyperkalemia, hypercoagulation, and increased CPK activity. The identified side effects of dexamethasone therapy most likely contributed to higher mortality in this group of animals.

When prescribing glucocorticoid therapy, especially at high doses, it is necessary to monitor the level of glucose, electrolytes, and the state of the blood coagulation system and timely correct the identified pathological changes, since these changes can significantly contribute to the development of ARDS.

REFERENCES

1. Minakov A.A., Salukhov V.V., Kharitonov M.A., Zagorodnikov G.G., Voloshin N.I. Some features of the course of viral pneumonia in obesity. *Medical Advice*. 2022;16(18):131–140(inRuss.).DOI:10.21518/2079-701X-2022-16-18-131-140.
2. Matute-Bello G., Frevert C.W., Martin T.R. Animal models of acute lung injury. *Am. J. Physiol. Lung Cell Mol. Physiol.* 2008Sept.;295(3):L379–L399. DOI: 10.1152/ajplung.00010.2008.
3. Mokra D., Mikolka P., Kosutova P., Mokry J. Corticosteroids in acute lung injury: the dilemma continues. *Int. J. Mol. Sci.* 2019Sept.25;20(19):4765. DOI: 10.3390/ijms20194765.
4. Yang J.W., Mao B., Tao R.J., Fan L.C., Lu H.W., Ge B.X. et al. Corticosteroids alleviate lipopolysaccharide-induced inflammation and lung injury via inhibiting NLRP3-inflammasome activation. *J. Cell Mol. Med.* 2020Nov.;24(21):12716–12725. DOI: 10.1111/jcmm.15849.
5. Qin M., Qiu Z. Changes in TNF-α, IL-6, IL-10 and VEGF in rats with ARDS and the effects of dexamethasone. *Experimental and Therapeutic Medicine.* 2019Jan.;17(1):383–387. DOI: 10.3892/etm.2018.6926.
6. Yang J.W., Mao B., Tao R.J., Fan L.C., Lu H.W., Ge B.X. et al. Corticosteroids alleviate lipopolysaccharide-induced inflammation and lung injury via inhibiting NLRP3-inflammasome activation. *J. Cell Mol. Med*. 2020Nov.;24(21):12716–12725. DOI: 10.1111/jcmm.15849.
7. Kim S.M., Min J.H., Kim J.H., Choi J., Park J.M., Lee J. et al. Methyl p-hydroxycinnamate exerts anti-inflammatory effects in mouse models of lipopolysaccharide-induced ARDS. *Mol. Med. Rep.* 2022Jan.;25(1):37. DOI: 10.3892/mmr.2021.12553.
8. Al-Harbi N.O., Imam F., Al-Harbi M.M., Ansari M.A., Zoheir K.M., Korashy H.M. et al. Dexamethasone attenuates LPS-induced acute lung injury through inhibition of NF-κB, COX-2, and pro-inflammatory mediators. *Immunol. Invest.* 2016May;45(4):349–369. DOI: 10.3109/08820139.2016.1157814.
9. Shekunova E.V., Kovaleva M.A., Makarova M.N., Makarov V.G. Dose selection in preclinical studies: cross-species dose conversion. *The Bulletin of the Scientific Centre for Expert Evaluation of Medicinal Products.* 2020; 10(1): 19–28 (in Russ.). DOI: 10.30895/1991-2919-2020-10-1-19-28.
10. Voloshin N.I., Pugach V.A., Tyunin M.A., Strokina E.I., Khizha V.V., Nikolaev A.V., Salukhov V.V. Clinical, biochemical and pathomorphological features of direct acute lung injury in rats caused by intratracheal administration of *Salmonella enterica lipopolysaccharide. Laboratory Animals for Science.* 2022;(3):16–23 (in Russ.). DOI: 10.57034/2618723X-2022-03-02.
11. Pugach V.A., Tyunin M.A., Ilyinsky N.S., Levchuk E.V., Strokina E.I., Yeltsov A.A. An experimental model of direct acute lung injury in rats caused by intratracheal administration of lipopolysaccharide from *Salmonella enterica. Biomedicine.* 2021;17(3):84–89 (in Russ.). DOI: 10.33647/2074-5982-17-3-84-89.

Authors' contribution

Salukhov V.V., Tyunin M.A. – conception and design, final approval of the manuscript for publication. Voloshin N.I., Levchuk E.V., Minakov A.A. – carrying out of the experiment, analysis and interpretation of the data. Voloshin N.I., Pugach V.A., Ilyinskiy N.S. – justification of the manuscript or critical revision of the manuscript for important intellectual content.

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