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Research Article

Role of Oxidized Dextran in Prevention and Control of Viral Pneumonia and Pulmonary Fibrosis

AV Troitsky[1], LA Cherdantseva[3], TN Bystrova[1], EG Novikova[1,2]*, HU Ukah[1], OV Grishin[1] and EA Lyadov[4]

[1]*Federal Medical Research Centre of Fundamental and Translational Medicine, Novosibirsk, Russia*

[2]*Regional Medical and Diagnostic Centre Ltd., Novosibirsk, Russia*

[3]*Novosibirsk Research Institute of Traumatology and Orthopedics n.a. Ya.L. Tsivyan, Novosibirsk, Russia*

[4]*St. Petersburg Tuberculosis Sanatorium "Pinery", Saint Petersburg, Russia*

***Corresponding Author:** EG Novikova, Federal Medical Research Centre of Fundamental and Translational Medicine, Novosibirsk, Russia.

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Abstract

Rationale for the Study: The relevance of the study is due to the large number of fibrous complications in viral interstitial pneumonia in COVID-19 patients in where …. Pulmonary fibrosis develops most often.

Objective of the Study: Title of the study to evaluate Role of Oxidized Dextran In Prevention and Control of Viral Pneumonia and Pulmonary Fibrosis

Specifically the therapeutic efficacy of inhalation administration of 2% oxidized dextran solution in an *in vivo* model that mimics interstitial pneumonia in COVID-19.

Materials and Methods: The studies were performed on mice of the ACR line. And interstitial pneumonia in mice was caused by intranasal administration of the lipopolysaccharide *Escherichia coli* (LPS). After intranasal administration of LPS to mice and legalization of a 2% solution of oxidized dextran and a control solution (physiological solution), they were carried out using an ultrasonic inhaler. A day later, the animals were slaughtered and prepared standard histological sections of lung tissue, followed by morphometric evaluation of the results.

Results with Data: inhalation administration of a 2% solution of oxidized dextran can almost 2 times reduce all morphological manifestations of LPS induced pneumonia by morphometric indicators: histe density of vessels with signs of hemocirculatory disorders, numerical density of thrombosed vessels, percentage of thrombosed vessels, volumetric density of hemorrhages, volumetric density of hemorrhages atelectasis, and volumetric density of cellular inflammatory infiltrate).

Conclusion: And the administration of oxidized dextran solutions may be a very promising method of preventing pulmonary fibrosis in COVID-19.

Keywords: Oxidized Dextran; Pneumonia; Pulmonary Fibrosis; Prevention and Control; COVID 19

Introduction

By the fall of 2021, almost 7 million cases of COVID-19 were registered in Russia, and the mortality rate was 2.65%. To date, it has been established that the SARS-CoV-2 virus causes lung damage in most patients, which can occur with computed tomography (CT) even before the appearance of positive laboratory tests and a detailed clinical picture [4]. According to a meta-analysis, based on CT of 2150 patients, changes in the type of «frosted glass» were found in 78% with mild and moderate severity, and infiltrative changes (according to the type of «consolidation») - in 34%, while in patients with a severe form of the course - in 82 and 61%, respectively [3].

One of the complications of COVID-19 pneumonia [4] and acute respiratory distress syndrome (ARDS) is pulmonary fibrosis [4,5]. Although the incidence and mechanism of lung fibrosis are not yet precisely understood, it is known that fibrosis develops in about 1/3 of patients admitted to specialized «covid» hospitals [1,2]. Given that pulmonary fibrosis can develop in non-hospitalized patients, it is obvious that this complication is much more widespread. Thus, there is a growing problem of destructive pulmonary pathology with severe residual pulmonary fibrosis and prolonged or even constant oxygen dependence, which greatly increases the load on the pulmonary level of health care.

The experience of treating post-Covid fibrosis abroad is limited to the scheme used in idiopathic pulmonary fibrosis (IAP) and includes tyrosine kinase inhibitors that block intracellular signaling important for the proliferation, migration and transformation of fibroblasts, representing the main pathological mechanisms of idiopathic pulmonary fibrosis [6]. Drugs are registered in Russia, but their high cost significantly limits their widespread use.

Another approach to problems is proposed in the UK [6]. It is based on the use of steroid therapy with prednisone in patients with advanced pneumonitis from the 1st week of acute COVID-19. The authors believe that such tactics reduce the likelihood of pulmonary fibrosis and contribute to the gradual restoration of external respiratory function.

The current Russian recommendations [7] note that «after suffering COVID-19, many patients in the lungs form pronounced changes in the form of fibrosis.» However, methods of prevention and/or treatment have not yet been presented.

There is a domestic drug «Longidase», in the indications for use of which pneumofibrosis, interstitial pneumonia and fibrosing alveolitis are indicated. It is assumed that the active ingredient of Longidase - bovgialuronidase azoximer depolymerizes glycosaminoglycans, thereby reducing tissue swelling, «flattening scars» and «having a smaller adhesion process» [8]. The effectiveness of Longidase in relation to the formation of fibrosis in the model of development of pulmonary pneumofibrosis in rats was shown in the works [10,11], however, the doses used were 10 times higher than those recommended for use in humans, taking into account the equivalent conversion.

At the same time, in the only available on the clinical publication [9], the use of Longidase against the background of glucocorticosteroids was shown only with fibrosing alveolitis in 30 patients compared with 15 patients of the comparison group. The use of Longidase for 6 months for a number of clinical and functional parameters showed a significantly positive trend, while in the control group, the opposite trend was observed. At the same time, longidase is not mentioned in clinical recommendations, nor recent work on the treatment of fibrosing interstitial lung diseases [12].

Thus, the increasing prevalence of pulmonary fibrosis, which limits the function of external respiration and forms the basis for such disabling diseases as chronic obstructive pulmonary disease and emphysema, poses a serious threat and requires the search for effective means for both the prevention and treatment of this complication.

One of these agents affecting all links in the pathogenesis of viral pneumonia with ARDS and pulmonary fibrosis may be oxidized dextran. Oxidized dextran is the most promising polysaccharide carrier for the immobilization of enzymes, pharmacological substances and, due to its properties, can be used to create various dosage forms with high anti-inflammatory and antifibrotic activity in combination with minimal toxicity to living cells of the body. Of Fundamental and Translational Medicine, a series of preclinical studies was conducted *in vivo* and *in vitro* for the comprehensive study of oxidized dextran and pharmaceutical substances immobilized on it for the treatment and prevention of pathological processes of various etiopathogenesis. The result of these studies was the choice of oxidized dextran as a biodegradable carrier for

immobilization of isonicotinic acid hydrazide and the creation of a complex anti-tuberculosis drug «Dextrazid», which in the course of preclinical trials showed high therapeutic and anti-inflammatory efficacy in combination with high antifibrotic, activity and low toxicity. Especially effective was the liposomal form of this drug «Dextrazid LF», which turned out to be effective not only with parenteral, but also with the inhalation method introduction [13-15]. The main pharmacological advantage of these agents is the ability of oxidized dextran to deliver the tuberculostatic drug ioniazid immobilized on it to macrophages due to receptor-mediated endocytosis. As is known, it is macrophages due to the incompleteness of phagocytosis that are the classic focus of persistence of the intracellular population M. tuberculosis. Due to the effect of selective vector delivery of the anti-tuberculosis drug, a high therapeutic efficacy of the new pro-duotuberculous drug is achieved.

In addition, it was found that oxidized dextran has a very valuable pharmacological property - the ability to activate macrophages. This helps to increase the secretion of anti-inflammatory cytokines by macrophages. In macrophages activated by oxidized dextran, the frequency of phagosomal-lysosomal fusions increases many times, which avoids the development of the phenomenon of incompleteness of phagocytosis - the basis of chronicity of pathological processes, one of the reasons for which is the intracellular persistence of an infectious agent (mycobacteriosis, candidiasis and viral infections).

In addition to these properties, oxidized dextran has a hepatoprotective effect, which was found in *in vivo* models [16,17]. In combination with the ability of oxidized dextran to activate macrophages, the above pharmacological properties can be used to develop effective treatments and prevent complications of acute respiratory viral infections (ARVI), in particular in influenza caused by highly pathogenic H5N1 and H1N1 strains, which has been confirmed in experimental models [17].

In connection with the above, the aim of this study is to study *in vivo* the effect of oxidized dextran in its inhalation method of administration on the development of structural changes in the lungs of mammals in experimental modeling of lung tissue damage caused by the SARS-CoV-2 virus with a possible assessment of the prospect of creating drugs based on oxidized dextran for use in complex therapy and as a means of prevention. viral interstitial pneumonia and pulmonary fibrosis.

Materials and Methods

Materials

Methods and methodology

Study design, study substances, target study substances, sample size calculation analysis and presentation, Oxidized dextran with m.M. 40 kDa was prepared by the modified method described in the patent RU 2618341, publ. 03.05.2017 Bul. №13. For inhalation administration, mice were prepared with a 2% aqueous solution of oxidized dextran.

As a biological model for assessing the anti-inflammatory efficacy of oxidized dextran in mammals, an *in vivo* model of interstitial pneumonia induced by intranasal administration of the lipopolysaccharide *Escherichia coli* (LPS) was chosen [18].

All *in vivo* studies were performed on 30 male ACR mice with an average body weight of 20-25 g. The animals were obtained from the nursery of the FBUN SSC VB «Vector» (Novosibirsk) and during the 14-day quarantine and throughout the study were in standard conditions, on a standard laboratory diet with free access to water and feed.

Before the study, the animals were divided into 3 groups:

- Group 1 (n = 10) - healthy mice of the ACR line 24 hours after a single intranasal administration of 20 µl of 0.9% NaCl solution and subsequent withdrawal from the experiment after 24 hours;
- Group 2 - control - male mice of the ACR line with intranasal administration of 20 µl of LPS solution (2 mg/ml) and subsequent withdrawal from the experiment after 24 hours;
- Group 3 - male mice of the ACR line with intranasal administration of 20 µl of LPS solution (2 mg/ml) followed by inhalation administration of 2% oxidized dextran solution with m.M. 40 kDa for 5 min. and withdrawal from the experiment after 24 hours.

Animals were removed from the experiment under ether anesthesia by dislocation of vertebrae in the cervical region. The object of the study was histological samples (sections) of tissue of the lower lobe of the right lung of mice of the ACR line of these

research groups. Visualization was carried out by direct light microscopy using a biological direct microscope AxioImager A1 with a camera AxioCam MRc5 («Carl Zeiss», Germany) with the tools of the program AxioVision (rel. 4.12) at magnification x 100, x 200.

For light-optical examination, the obtained material was fixed in a 10% solution of neutral formalin, dehydrated in a series of alcohols of increasing concentration and xylenes, followed by imprisonment in paraffin. Sections with a thickness of 4-5 μm were made and stained according to the standard technique with hematoxylin and eosin. In sections of mouse lung tissue samples, the following histological signs of pathological changes were evaluated: the severity of interstitial and alveolar edema, hemocirculatory disorders, cellular inflammatory infiltration, destructive changes (emphysema sites, atelectasis, dystrophic and necrotic changes in the bronchial epithelium). Morphometry of the structural elements of tissues was carried out using an ocular mesh for 100 points with an area of 3.64x104 μm2 (when determining the numerical and/or volume density of structures) and the tools of the AxioVision program (rel. 4.7).

The obtained morphometric data were subjected to statistical processing and analysis using the software package «Statistica 10.0» («Statsoft») with the determination of average values and errors of the average for each study group, determined the reliability of the differences in the compared averages using the Student t-criterion, at $p < 0.05$.

The biological experiment was conducted in accordance with the National Standard of the Russian Federation «Principles of Good Laboratory Practice», approved and put into effect by the Order of Rostekhregulirovanie dated 02.12.2009 (No. 544-st, GOST R 53434-2009) and in compliance with the international principles of the Helsinki Declaration.

Findings

During histological examination of samples of lungs of animals of the control group, it was revealed that the lumens of the bronchi of different calibers, up to the bronchioles and the lumens of the alveoli are free, signs of damage to the bronchial and alveolar epithelium, as well as hemocirculatory disorders are absent.

Histological examination of samples of lungs of animals with LPS-induced inflammation revealed focal moderate and pronounced inflammatory infiltration of the walls of the bronchi and interalveolar septa with their expansion and the formation of foci of atelectasis. At the same time, the cellular inflammatory infiltrate was lymphocytic-macrophage in nature with single neutrophils. In addition, the formation of alveolar macrophages with «foamy» cytoplasm was revealed (Figure 1a, 1b).

Figure 1a: Fragment of lung mouse tissue ACR 24 hours after inhalation administration of LPS - lymphocytic-macrophage infiltration of interalveolar septa, with single neutrophils and the formation of alveolar macrophages with "foamy" cytoplasm; focal destruction of interalveolar septa. Coloration with hematoxylin and eosin. Increase x 400.

Figure 1b: A fragment of lung mouse tissue ACR 24 hours after inhalation administration of LPS - focal moderately pronounced lymphocytic-macrophage infiltration of the walls of the bronchi; focal hyperplasia of the bronchial epithelium with areas of pseudo-multi-row epithelium, deformation of the lumen of the bronchi; moderate fullness of blood vessels; focal expansion of the interalveolar septa due to edema and cellular inflammatory infiltration of a lymphocytic-macrophage nature with single neutrophils, foci of atelectasis; focal diapedesis hemorrhagic impregnation of interalveolar septa. Coloration with hematoxylin and eosin. Magnification x 100.

Also in the lungs of animals of this group, focal weak and moderate edema of the walls of the bronchi, moderate and focal pronounced hyperplasia of the bronchial epithelium with the formation of areas of pseudo-multi-order epithelium, foci of micronecrosis and accumulation of serous exudate in the lumen of the bronchi of medium and small caliber were revealed. This was accompanied by deformation and narrowing of the lumens of the bronchi (Figure 1b).

In addition, in the lungs of animals of this group, focal destruction of the interolveolar septa was revealed with the formation of areas of emphysematous changes in the lung tissue (Figure 2).

Figure 2: A fragment of lung tissue ACR 24 hours after inhalation administration of LPS - focal pronounced hyperplasia of the hypersecretory epithelium of the bronchus; peribronchial areas of emphysematous changes in lung tissue; focal perivascular moderately pronounced edema; focal diapedesis hemorrhage. Coloration with hematoxylin and eosin. Magnification x 200.

In addition to focal moderate and pronounced fullness of blood vessels of different calibers in animals with LPS-induced lesions in the lung tissue, thrombosis, mainly of small vessels, the formation of focal perivascular edema and areas of hemorrhage were detected (Figure 3, 4).

In lung samples of mice with treatment of LPS-induced lung damage with oxidized dextran-40 kDa (group 3), weak and focal moderately pronounced lymphocytic-macrophage infiltration of the walls of the bronchi and interalveolar septa with single neutrophils was revealed. In various parts of the bronchial tree,

Figure 3: A fragment of lung tissue ACR 24 hours after inhalation administration of LPS - pronounced fullness and thrombosis of small-caliber lung vessels; areas of emphysematous changes in lung tissue; focal thickening of the interalveolar septa with their lymphocytic-macrophage infiltration. Coloration with hematoxylin and eosin. Magnification x 200.

these changes were accompanied by focal weak and moderate hyperplasia of the bronchial epithelium (Figure 4a).

This was accompanied by a smaller scale of focal destructive changes in the lungs of animals of this group in the form of areas of destruction of interalveolar septa with the formation of focal emphysema, alternating with areas of atelectasis (Figure 4a, 4b).

Figure 4a: Fragment of lung mouse ACR tissue with LPS-induced lung damage and subsequent inhalation administration of a solution of oxidized dextran-40 kDa, 1 day of study: weak lymphocytic-macrophage infiltration of the bronchial walls and focal moderate cell inflammatory infiltration of the interalveolar septa. Staining with hematoxylin and eosin. Increase x 100.

Figure 4b: Fragment of ACR lung mouse tissue with LPS-induced lung damage and subsequent inhalation administration of an oxidized dextran-40 kDa solution, 1 day of study: moderate lymphocytic-macrophage infiltration of interalveolar septa with single neutrophils; foci of emphysema and areas of atelectasis. Coloration with hematoxylin and eosin. Increase x 200.

The severity of these morphological changes was less in comparison with the severity of similar pathological changes in animals of group 2 of the study.

At the same time, the value of the volume density of atelectasis in animals of group 3 was 2 times less than in animals of group 2, and the volume density of cellular inflammatory infiltrate was 1.6 times less (Table 1).

Study parameters	Study Groups		
	1 group	Group 2	Group 3
Numerical density of vessels with signs of hemocirculatory disorders, (Nai)	___	23,75 ± 4,33	12,45 ± 3,86*
Numerical density of thrombosed vessels	___	7,62 ± 1,24	2,55 ± 1,51*
% of thrombosed vessels	___	32,1	20,5
Volumetric density of hemorrhages, (Vv)	___	6,75 ± 1,25	2,54 ± 0,21*
Bulk density of atelectases, (Vv)	___	20,37 ± 2,77	10,36 ± 4,99*
Bulk density of cellular inflammatory infiltrate, (Vv)	___	35,63 ± 5,50	22,63 ± 8,26

Table 1: Structural changes in the lungs of ACR line mice with LPS-induced lung damage and when treated with an inhaled form of oxidized dextran-40 kDa (M+m).

Note: * - reliability of differences in the values of the compared parameters relative to the group of animals with LPS-induced lung damage (group 2).

In addition, in the lungs of mice in the treatment of LPS-induced lung damage with an inhaled form of oxidized dextran - 40 kDa, as well as in mice that did not receive treatment, hemocirculatory disorders were detected, which were less pronounced than in animals of group 2 and were focal, mainly moderately pronounced in nature and were accompanied by thrombosis of single small vessels of the lungs and the formation of focal weak perivascular and peribronchial edema, as well as minor areas of diapedesis hemorrhages (Figure 5a, 5b).

Figure 5a: Fragment of lung tissue of the ACR mouse with LPS-induced lung damage and subsequent inhalation administration of a solution of oxidized dextran-40 kDa on the 1st day of the study: weak focal hyperplasia of the bronchial epithelium; weak lymphocytic-macrophage infiltration of the interalveolar septa with single neutrophils; moderate vascular fullness. Coloration with hematoxylin and eosin. Increase x 100.

Figure 5b: Fragment of lung mouse ACR tissue with LPS-induced lung damage and subsequent inhalation administration of a solution of oxidized dextran-40 kDa on the 1st day of the study: lymphocytic-macrophage infiltration of interalveolar septa with single neutrophils; moderate vascular fullness with the formation of blood clots in individual small vessels. Coloration with hematoxylin and eosin. Increase x 200.

At the same time, the value of the numerical density of lung vessels with signs of hemocirculatory disorders in animals of group 3 was 1.9 times less than in mice of group 2 (Table 1). This was accompanied in animals during inhalation treatment of LPS-induced lung damage by the formation of significantly lower indicators of numerical density in the lung tissue of thrombosed vessels (3 times) and volumetric density of diapedesis hemorrhages (2.7 times).

Discussion and Conclusion

Discuss your results and findings in relation to other studies. As can be seen from the presented results of a single inhalation of a 2% solution of oxidized dextran is sufficient to realize the pronounced protective properties of this agent against the structural elements of the lung tissue in LPS-induced interstitial pneumonia. Taking into account that the selected model of experimental interstitial pneumonia is recognized as the optimal model for the reproduction of structural damage to the lungs of mammals [4] and, in particular, humans, caused by the SARS-CoV-2 virus, the potential significant prospects of an inhalation method for administering an oxidized dextran solution as a drug in a complex therapy and for the prevention of lung damage in coronavirus infection. At the same time, the absence of toxicity and oxidized dextran at a pair of ternal administration in doses hundreds of times higher than the dose with its inhalation method of administration, allows us to count on maximum clinical safety of the use of dosage forms based on this agent. In this regard, irrigation of the mucous membranes of the upper respiratory tract with an aerosol form of a 2% solution of oxidized dextran, which has the ability to activate, including alveolar macrophages, can be an effective daily remedy for the prevention of COVID-19, and inhalations of a 2% solution of oxidized dextran are most appropriate for the prevention of pulmonary complications of COVID-19.

It should be noted that the therapeutic efficacy of inhalation administration of a 2% solution of oxidized dextran is manifested in all pathophysiological links in the development of interstitial pneumonia and acute respiratory distress syndrome (ARDS). In particular, there is a distinct 2-fold regression of hemocircular disorders, which are known to dominate in viral interstitial pneumonia and ARDS, moreover, these disorders usually form a symptom complex of disseminated intravascular coagulation. A similar therapeutic effect is also confirmed by an almost 3-fold decrease in the volumetric density of hemorrhages in the lung tissue. Thus, it can be expected that inhalation administration of oxidized dextran will effectively prevent the development of DIC syndrome in viral interstitial pneumonia and ARDS. In this aspect, attention is also drawn to a sharp decrease in the percentage of thrombosed vessels in the lung tissue during inhalation of a solution of oxidized dextran. This may indicate an indirect thrombolytic effect of the drug due to the receptor for indirect activation of alveolar macrophages and an increase in their production. tissue proteinases, which are endogenous fibrinolytic components. Such a circumstance is very important from the pathomorphological and pathophysiological points of view, since it has been established that the development of DIC syndrome with thrombotic complications is one of the main links in the pathogenesis of lung damage in pneumonia caused by the SARS-CoV-2 virus. The pronounced therapeutic effect of oxidized dextran in LPS-induced pneumonia, aimed at correcting hemocirculatory disorders, reducing the volumetric density of hemorrhages and the percentage of thrombosed vessels, can be a priority vector in the treatment of viral pneumonia and ARDS,

as it is aimed at key links in the pathogenesis and mechanisms of disease development. Also, on the basis of the data obtained, it can be argued about the high anti-inflammatory effect of the solution of oxidized dextran when it is inhaled, which is confirmed by a decrease in the volume density of the cellular inflammatory infiltrate in the lungs. Particularly promising from the point of view of treating pulmonary complications of COVID-19 is the almost 2-fold regression of the volumetric density of atelectasis foci on the LPS-induced pneumonia model.

Thus, the data obtained allow us to consider the inhalation administration of oxidized dextran potentially very promising for the prevention and treatment of pneumonia caused by the SARS-CoV-2 virus. At the same time, the previously identified antifibrotic efficacy of oxidized dextran and the mechanisms of its implementation, in relation to this pathological process, require further comprehensive study. We believe that the antifibrotic effect is also mediated by the increased production of tissue hydrolases, including collagenases, by alveolar macrophages activated by oxidized dextran. As is known, pulmonary fibrosis is the main factor in severe damage to lung tissue in interstitial pneumonia caused by SARS-CoV-2. Currently, the arsenal of drugs to combat pulmonary fibrosis after viral pneumonia is very limited and the use of inhalation administration of solutions of oxidized dextran will significantly increase the effectiveness of treatment of this severe complication of acute respiratory viral infections. Currently, glucocorticoids are mainly used to treat pulmonary fibrosis. Their effectiveness is relatively low and they have a pronounced side effect (violation of calcium metabolism, increased blood pressure, exacerbation of gastric ulcer, etc.). The mechanism of action of glucocorticoids is aimed only at suppressing fibrogenesis by reducing fibroblast proliferation and reducing collagen synthesis. They do not contribute to the involution of fibrous tissue and therefore are considered only as means of preventing the progression of pulmonary fibrosis. Oxidized dextran has a combined therapeutic effect. On the one hand, it inhibits the development of fibrous tissue in the lungs by reducing inflammation and improving hemodynamics. In this respect, it can be considered as an effective means of preventing pulmonary fibrosis. On the other hand, oxidized dextran activates tissue macrophages in the lungs that secrete tissue proteinases. Tissue proteinases are able to lyse fibrous tissue. In this respect, oxidized dextran can be considered as a therapeutic drug. Oxidized dextran, unlike glucocorticoids, has no side effects, is non-toxic and does not cause allergic reactions. In this regard, oxidized dextran can be recommended for a wide range of patients, without any contraindications.

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