Int J Clin Exp Med 2020;13(9):7098-7105
www.ijcem.com /ISSN:1940-5901/IJCEM0107596

Original Article

Protective effect of dexmedetomidine in rats with acute lung injury and its mechanism

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Received January 8, 2020; Accepted July 11, 2020; Epub September 15, 2020; Published September 30, 2020

Abstract: Objective: We aimed to analyze the protective effect of dexmedetomidine (Dex) in rats with acute lung injury (ALI) and its mechanism. Methods: A total of 40 healthy adult SD rats were selected and randomly divided into a normal group (NG), a model group (MG), a high-dose dexmedetomidine (Dex4.5) group (Dex4.5G), a medium-dose dexmedetomidine (Dex1.5) group (Dex1.5G) and a low-dose dexmedetomidine (Dex0.5) group (Dex0.5G); with 8 rats in each group. Corresponding treatments were performed in these groups for result analysis. Results: (1) The body mass (BM) was similar in five groups (P>0.05); the lung weight (LW) and organ coefficient (OC) of the MG and Dex0.5G were much higher than those of the NG (P<0.05); and those of the Dex1.5G and Dex4.5G were much lower than those of MG (P<0.05). (2) The lung wet weight/dry weight (WW/DW) ratio of the MG and Dex0.5G was much higher than that of the NG (P>0.05); and that of the Dex1.5G and Dex4.5G was much lower than that of the MG (P<0.05). (3) The levels of TNF-α, IL-1β and IL-6 in lung homogenate (LH) of the MG, Dex0.5G, Dex1.5G and Dex4.5G were much higher than those of the NG (P<0.05); those of the Dex1.5G and Dex4.5G were much lower than those of the MG (P<0.05); while those of the Dex0.5G were similar to those of the MG (P>0.05). (4) The degree of lung tissue injury (LTI degree) in the Dex0.5G, Dex1.5G and Dex4.5G was much lower than that of the MG according to pathological examination (P<0.05). (5) The NF-kB level was (19.88±5.09) in the NG, (35.76±8.94) in the MG, (32.49±6.89) in the Dex0.5G, (25.23±4.34) in the Dex1.5G and (21.13±5.39) in the Dex4.5G. (6) The TLR4 mRNA expression level was (0.39±0.03) in the NG, (0.61±0.05) in the MG, (0.60±0.04) in the Dex0.5G, (0.44±0.11) in the Dex1.5G and (0.31±0.08) in the Dex4.5G. Conclusion: The high and medium-dose Dex administration used for ALI rats can reduce OC and lung WW/DW ratio, achieve good protection for the alveolar membrane, alleviate interstitial edema and inflammatory cell infiltration and exudation, reduce the level of inflammatory factors and inflammation levels in the lung, and control NFkB protein and TLR4 mRNA expression; showing good protective effects in the lung.

Keywords: Acute lung injury, rat, dexmedetomidine, protective effect, mechanism

Introduction

Acute lung injury (ALI) is a type of progressive or acute hypoxic respiratory failure caused by different intrapulmonary and extrapulmonary pathogenic factors, but not from cardiogenic respiratory failure. Acute respiratory distress syndrome (ARDS) is the severe stage of ALI, including various pathogenic factors, which has a relatively high mortality rate [1].

Due to the sudden onset of ALI, it can rapidly cause multiple organ dysfunction syndrome (MODS), and without timely and effective treatment, it can lead to poor prognosis and has a high mortality risk [2]. In order to alleviate the hyperinflammatory response, protective treatment measures must be actively taken to effectively control the inflammatory level and improve the prognosis. Dexmedetomidine (Dex) is an α2 adrenergic agonist widely used in anesthesia and sedation. This drug is selective for stimulating α2 adrenergic receptors in central nervous system, and has the effects of analgesia, sedation and antisympathia [3]. It has been found clinically that the incidence of coma and delirium was obviously reduced in patients with mechanical ventilation after Dex

sedation [4]. Other research has shown that Dex greatly reduced the systemic inflammatory response (SIR) caused by endotoxins [5]. Current research has also indicated that Dex can effectively regulate the level of inflammatory factors [6].

Some studies have suggested that Dex has a protective effect on ALI, but its mechanism of action (MOA) is still unclear due to the lack of relevant studies, and the specific dose with the highest application value has not been clarified. Based on this, 40 healthy Sprague Dawley (SD) rats were selected for an *in vitro* study to analyze the protective effect of three different doses of Dex on ALI and to explore its specific MOA.

Material and methods

Materials

A total of 40 pathogen free SD rats were housed in individual cages and fed a standard rodent feed; with a humidity of 60-65% and a temperature of 21-23°C. All rats were allowed to eat and drink freely. The food and housing instruments of the rats were strictly disinfected and the cages and bedding were replaced every 2 days. This study was approved by the Affiliated Hospital of Shandong University of Traditional Chinese Medicine Laboratory Animal Centre and complied with ethical requirements.

Methods

Animal grouping: The rats were divided into a normal group (NG), model group (MG), low-dose Dex group (Dex0.5G), medium-dose Dex group (Dex1.5G) and high-dose Dex group (Dex4.5G); with 8 rats in each group.

Establishment of ALI models: The rats were weighed and intraperitoneally injected with 30 mg/kg 1% nembutal. An incision was made in the center of throat for trachea cannula after rats were fixed on experiment table. Then, autonomous respiration was maintained, the right femoral vein was incised, and the cannula was inserted for drug delivery. After half an hour, Dex0.5G, Dex1.5G and Dex4.5G were respectively injected at 0.5 μg/kg Dex, 1.5 μg/kg Dex and 4.5 μg/kg Dex within 10 min. After 5 min, the MG, Dex4.5G, Dex1.5G and Dex0.5G were intravenously injected with 4 mg/kg lipopolysaccharide (LPS) within 10 min at a low speed and the NG was injected with 0.5 ml/kg normal saline (NS) through the femoral vein. All groups were closely observed in respect of heartbeat, breathing rate, excrement and urine after corresponding treatments.

Measurements of body mass (BM) and lung weight (LW) and calculation of organ coefficient (OC) were made and then 100 mg/kg 1% nembutal was intraperitoneally injected 5 h after drug delivery. Rats were sacrificed through bloodletting of the aorta abdominalis. Then, the lung tissues were separated, placed on glacial table and photographed to record the appearance and morphology of tissues. The lung was washed with 4°C 0.9% sodium chloride solution, dried with filter paper, and weighed, and the OC was calculated. OC = WW/BM.

Preparation of lung homogenate (LH) and RT-PCR specimen: The lung tissues were retained and washed repeatedly with cold NS, dried with filter paper and then weighed. Next, 0.9% cold NS was added at the proportion of 1:9 and tissue was pulverized thoroughly to prepare a 10% tissue homogenate. After centrifugation for 10 min, the supernatant was extracted and stored in a freezer at -20°C. The temperature of tissue preparation was kept at 4°C during the whole process that lasted for 15 min.

Preparation of pathological specimens: The upper lobe of the right lung was retained, fixed with 10% formaldehyde solution, and embedded in routine paraffin for later immumohistochemical (IHC) staining and hemotoxylin and eosin (H&E) staining.

Observation measures

Lung wet weight/dry weight (WW/DW) ratio and OC: The blood in the lower lobe of the right lung was cleaned with filter paper to obtain the WW. Then, the lung tissues were dried for 72 h in an incubator (at 80°C) to obtain the DW. Finally, the WW/DW ratio of lung tissues was calculated and the degree of pulmonary edema (PE degree) was evaluated according to results.

Inflammatory level of LH: ELISA was used to measure the levels of TNF-α, IL-6 and IL-1β.

Histopathological observation: The upper lobe of the right lung was fixed with 10% formalde-

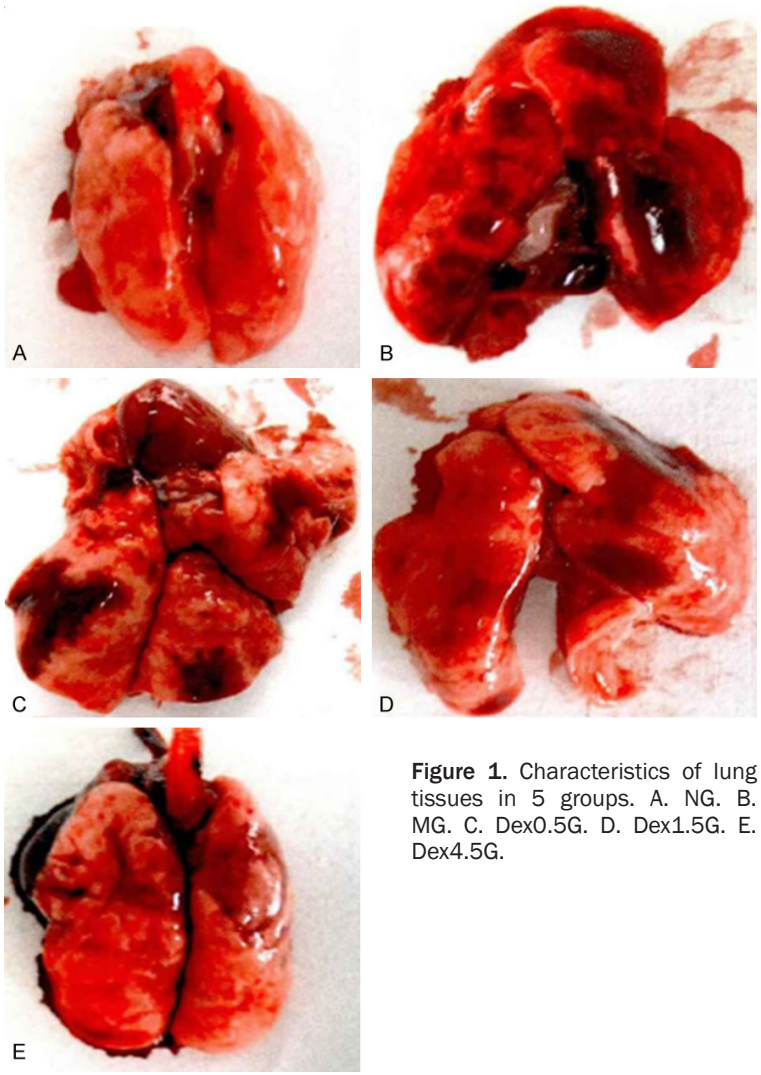

Figure 1. Characteristics of lung tissues in 5 groups. A. NG. B. MG. C. Dex0.5G. D. Dex1.5G. E. Dex4.5G.

hyde solution, dehydrated with gradient ethanol, embedded in paraffin, sliced and stained with H&E. Then, the light microscope was used for histopathological observation. H&E staining methods: 5 μm slices were dewaxed. Then, these slices were stained with hemotoxylin for 5 min, washed with running water for 1-3 s, differentiated with 1% hydrochloric acid ethanol for 1-3 s, washed with running water for 10 min to until blue, stained with eosin for 2 min, washed slightly with distilled water, dehydrated with ethyl alcohol, transparentized with xylene, and sealed with neutral resin.

Expression of NF-kB through IHC (SABN method) [7]: IHC SABC method was used for staining after slicing and the light microscope was used to observe the expression of NF-kB in lung tissues.

Expression of TLR4 mRNA through RT-PCR: RT-PCR [8] was used to detect the expression of TLR4 mRNA in lung.

Statistical analysis

SPSS 22.0 was used for statistical analysis. The measurement data were represented as mean ± standard deviation and the results between groups were compared through independent-samples *t* test. The enumeration data were represented as [n (%)] and the results between groups were compared through chi-squared test. The multi-point comparison in groups was performed through ANVOA and F test. $P<0.05$ meant that the difference was statistically significant.

Results

Observation on ALI rats

In the NG, it was found by opening the thoracic cavity that the normal lung tissues had smooth surface with a color of rose pink, without any infarction, edema and hyperaemia, and the elasticity was good. The lung tissues of the MG were dark red, with edema and obvious hyperaemia under the lung capsule and a wide range of bleeding spots. The elasticity was poor. The lung tissues of three Dex groups were dark red, with obvious edema and hyperaemia and scattered bleeding spots, but the bleeding spots were fewer than those of the MG. The higher dose of Dex indicated a milder LTI degree (**Figure 1**).

WW and OC of ALI rats

There was no significant difference in BM among five groups ($P>0.05$). The LW and OC of the MG and Dex0.5G were much higher than those of the NG ($P<0.05$); and those of the Dex1.5G and Dex4.5G were much lower than those of the MG ($P<0.05$) (**Table 1**).

Table 1. Influence of Dex on WW and OC of ALI rats ($\bar{x}$ ± s)

Group	BM (g)	LW (g)	OC
NG	196.23±9.15	1.24±0.11	6.06±0.51
MG	198.42±8.46	2.03±0.44*	9.08±2.13*
DEx0.5	196.38±10.08	2.02±0.51*	10.15±2.34*
DEx1.5	198.12±9.26	1.45±0.33$^{\&}$	7.35±1.25$^{\&}$
DEx4.5	199.23±9.87	1.41±0.22$^{\&}$	7.68±0.85$^{\&}$
F	0.527	2.986	3.251
P	0.139	0.027	0.018

Compared with NG, *P<0.05; compared with MG, $^{\&}P$<0.05.

Table 2. Influence of Dex on lung WW/DW ratio of ALI rats ($\bar{x}$ ± s)

Group	WW (g)	DW (g)	WW/DW
NG	0.23±0.14	0.050±0.031	4.71±0.39
MG	0.25±0.11	0.046±0.018	5.46±0.75*
DEx0.5	0.22±0.06	0.043±0.013	5.24±0.40*
DEx1.5	0.17±0.08	0.037±0.012	4.62±0.61$^{\&}$
DEx4.5	0.18±0.07	0.040±0.012	4.38±0.54$^{\&}$
F	0.428	0.362	2.857
P	0.108	0.089	0.031

Compared with NG, *P<0.05; compared with MG, $^{\&}P$<0.05.

WW/DW ratio of ALI rats

The WW/DW ratio of the MG and Dex0.5G was much higher than that of the NG (P>0.05); and that of the Dex1.5G and Dex4.5G was much lower than that of the MG (P<0.05) (**Table 2**).

Inflammatory level of ALI rats

The levels of TNF-α, IL-1β and IL-6 were respectively (167.45±28.85) pg/mg, (53.19±8.76) pg/mg and (42.95±10.37) pg/mg in the NG; (398.45±39.82) pg/mg, (87.99±8.65) pg/mg and (72.86±10.27) pg/mg in the MG; (359.85±42.34) pg/mg, (90.15±14.28) pg/mg and (72.62±10.39) pg/mg in the Dex0.5G; (313.28±82.16) pg/mg, (74.16±7.19) pg/mg and (44.95±15.38) pg/mg in the Dex1.5G; and (246.39±60.38) pg/mg, (73.49±9.15) pg/mg and (32.86±20.13) pg/mg in the Dex4.5G. The levels of TNF-α, IL-1β and IL-6 in LH of the MG, Dex0.5G, Dex1.5G and Dex4.5G were much higher than those of the NG (P<0.05); those of the Dex1.5G and Dex4.5G were much lower than those of the MG (P<0.05); and those of Dex0.5G were similar to those of the MG (P>0.05) (**Figure 2**).

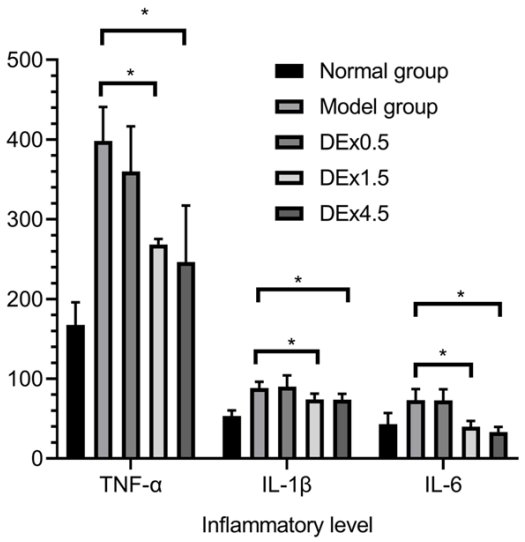

Figure 2. Comparison of inflammatory level among the five groups. The levels of TNF-α, IL-1β and IL-6 in the Dex1.5G and Dex4.5G were much lower than those in the MG (P<0.05). * meant P<0.05 when two groups were compared.

Pathological examination results of ALI rats

The light microscope examination showed that the lung tissue structure in the MG was seriously damaged, manifesting as alveolar hemorrhage, pulmonary interstitial edema, alveolar atrophy and inflammatory cell infiltration. By contrast, the lung tissues of the Dex0.5G, Dex1.5G and Dex4.5G were not so seriously damaged. The pulmonary septum was expanded slightly, the bleeding was not obvious, and the inflammatory cell infiltration was moderate. Therefore, the degree of damage of the lung tissues was the lowest in the Dex4.5G (**Figure 3**).

NF-kB expression in ALI rats

NF-kB level was (19.88±5.09) in the NG, (35.76±8.94) in the MG, (32.49±6.89) in the Dex0.5G, (25.23±4.34) in the Dex1.5G and (21.13±5.39) in the Dex4.5G. The cells that positively reacted for NF-kB included tracheal mucosal epithelial cells, inflammatory infiltration cells, alveolar epithelial cells and vascular endothelial cells. The NG showed a small number of positive cells of NF-kB in the nucleus of the tracheal mucosae and pulmonary interstitium. By contrast, there were more positive cells for NF-kB in the tracheal mucosae, pulmonary interstitium, alveolar space and vascular endothelial cells of the MG. The higher dose of Dex revealed fewer positive cells with NF-kB (**Figures 4** and **5**).

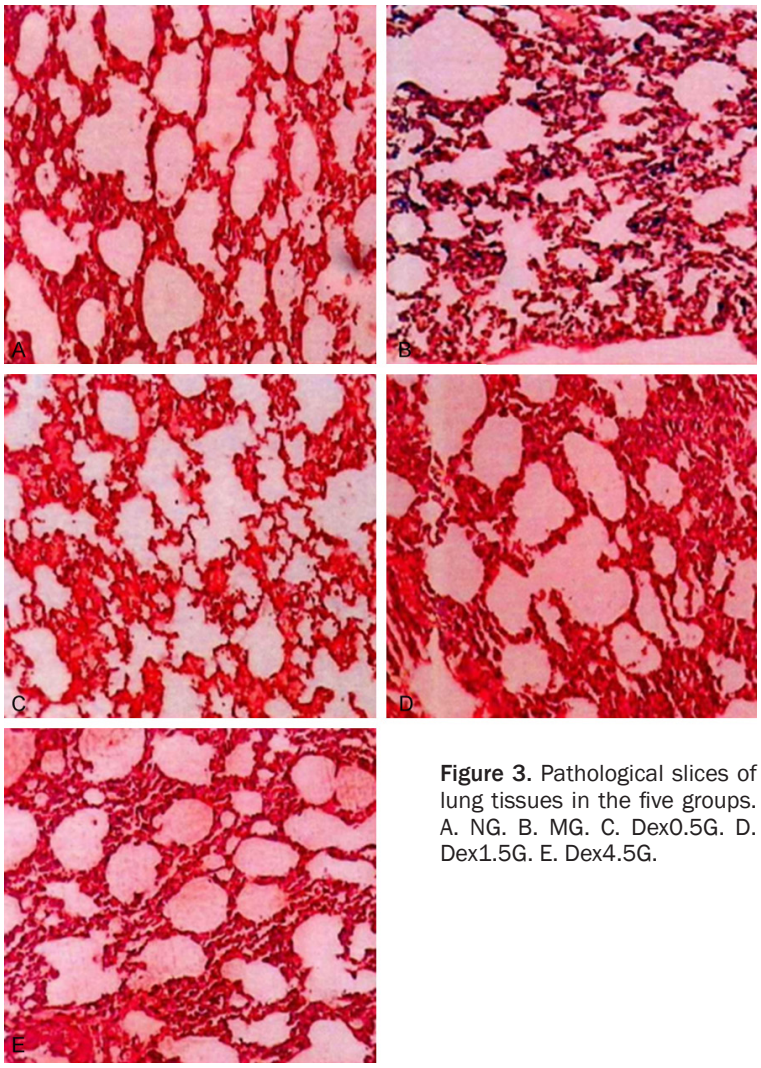

Figure 3. Pathological slices of lung tissues in the five groups. A. NG. B. MG. C. Dex0.5G. D. Dex1.5G. E. Dex4.5G.

Influence of TLR4 mRNA expression in lung tissues of ALI rats

The TLR4 mRNA expression level was (0.39±0.03) in the NG, (0.61±0.05) in the MG, (0.60±0.04) in the Dex0.5G, (0.44±0.11) in the Dex1.5G and (0.31±0.08) in the Dex4.5G. It was found through RT-PCR that the TLR4 mRNA expression level of the MG, Dex0.5G and Dex1.5G was much higher than that of the NG ($P<0.05$); that of the Dex4.5G was similar to that of the NG ($P>0.05$); and that of the Dex1.5G and Dex4.5G was much lower than that of the MG ($P<0.05$) (**Figure 6**).

Discussion

Clinically, ALI may be caused by intrapulmonary or extrapulmonary diseases, such as septicopyemia, cerebral contusion, fracture, peritonitis and pulmonary infection, *etc*. [9, 10]. The pathogenesis of ALI is still unclear. It may be caused by the increase of inflammatory levels and capillary permeability [11]. Many inflammatory cells will be activated after ALI, which leads to an uncontrolled inflammatory response, *i.e.* systemic inflammatory response syndrome [12]. The body will be damaged accordingly, which causes the activation of more inflammatory cells and the release of more cell factors and inflammatory mediators. Then, the body will be damaged more as the inflammatory cascade response occurs. Thus, more organs are damaged. So it is very important to control the inflammatory level in ALI patients [13, 14].

Dex can stimulate α2 receptors in presynaptic membrane of neurons, inhibit the release of norepinephrine and thus terminate the transduction of pain signals [15]. This analgesic effect is achieved through Dex activation of neurons in the brain and spinal cord. Besides, it can reduce the dose of anaesthetics, enhance the haemodynamic stability and decrease the incidence of myocardial ischaemia [16]. Clinically, Dex is considered to have good analgesic effects and does not inhibit patients' autonomous respiration, so it is widely used in operations. Besides, Dex has been clinically proven to reduce the incidence of postoperative delirium and agitation or lessen the severity of these responses [17, 18]. Based on intensive studies in recent years, some scholars have found that this drug can alleviate the systemic inflammatory response caused by endotoxins and reduce the incidence of ALI caused by large tidal volume ventilation [2, 19].

Through the observation of lung tissues in five groups of differentially treated rats, it was found in this study that the lung tissue became

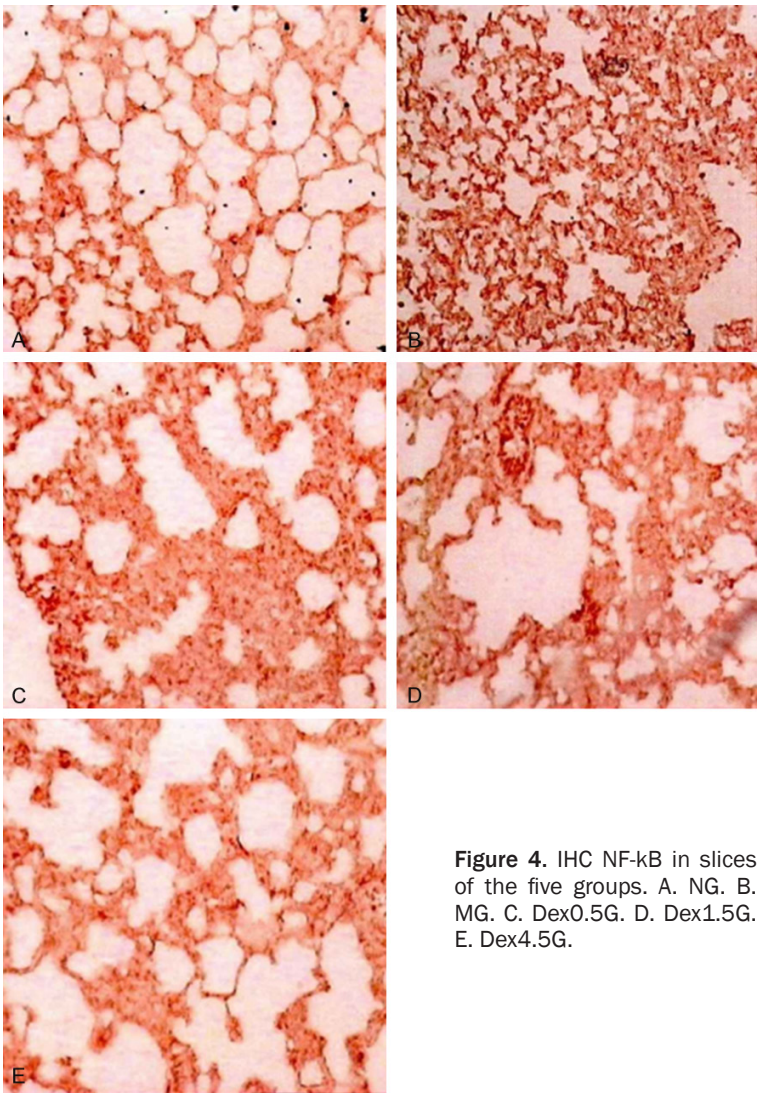

Figure 4. IHC NF-kB in slices of the five groups. A. NG. B. MG. C. Dex0.5G. D. Dex1.5G. E. Dex4.5G.

darker in ALI rats, with edema and hyperaemia in the lung capsule and with a wide range of bleeding spots. The elasticity of the tissue was also reduced. Dex alleviated the edema and hyperaemia in the lung capsule, reduced the number of bleeding spots and enhanced the tissue elasticity. The higher dose of Dex resulted in more normal lung tissue. In addition, the LW, OC and lung WW/DW ratio was reduced more significantly after treatment in the Dex1.5G and Dex4.5G than in the MG, but the changes were not significantly in the Dex0.5G. This implied that the high and medium-dose Dex can greatly reduce the PE degree of ALI rats. The higher dose resulted in more significant tissue health. This study also showed that the levels of TNF-α, IL-1β and IL-6 in the Dex1.5G and Dex4.5G were much lower than those in the MG and the level of inflammatory factors changed slightly in the Dex0.5G. This indicated that Dex can effectively control and significantly down-regulate the inflammatory level in ALI rats. The higher the dose resulted in a better controlled inflammatory state. Pathological examination showed that the lung tissue structure was damaged significantly after ALI, and Dex could alleviate LTI. The higher dose resulted in a milder LTI degree. This implied that Dex can significantly protect the lung tissue conditions in ALI. The measurement of NF-kB expression showed that Dex significantly reduced the NF-kB expression in lung tissues of ALI rats and decreased the positive rate cells with NF-kB in the nucleus. The measurement of TLR4 mRNA expression through RT-PCR showed that Dex down-regulated the TLR4 mRNA expression level in lung tissues of ALI rats. The higher dose resulted in a more obvious down-regulation of NF-kB and TLR4 mRNA expression.

Dex can alleviate LTI and down-regulate the inflammatory level and NF-kB and TLR4 mRNA expression by reducing the level of inflammatory factors, thus further alleviating the systemic inflammatory response. Therefore, the damage of alveolar cells and pulmonary vascular epithelial cells can be alleviated, and the synthesis and release of pulmonary surfactant can be accelerated, thereby reducing the degree of LTI [20, 21]. Furthermore, Dex can alleviates the interaction between inflammatory cell factors and white blood cells (WBC) and the excessive activation of WBCs, thus reducing the damage of WBC [22]. Dex can also inhibit the generation of oxygen radicals, alleviate damage to cellular structures and vascular endothelial cells, and finally reduce the degree of pulmonary exudation and PE [23]. High-dose Dex can combine with α1 adrenergic receptor to enhance the

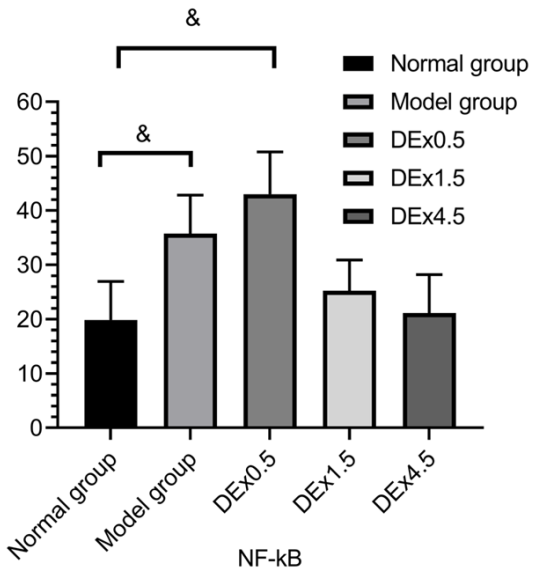

Figure 5. Comparison of NF-kB level among the five groups. The NF-kB level of the MG and Dex0.5G was much higher than that of the NG (P<0.05). & meant P<0.05 when two groups were compared.

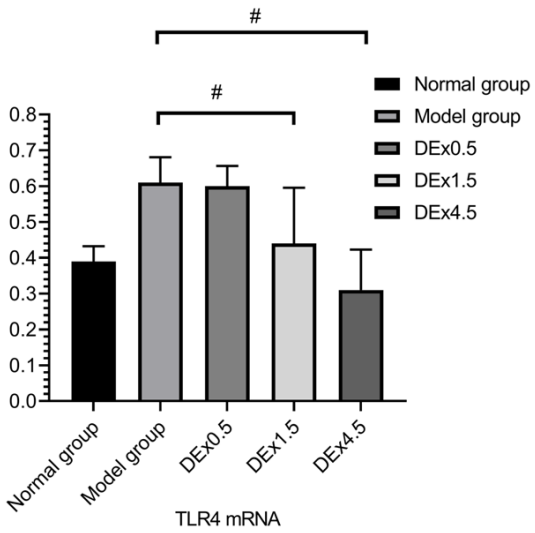

Figure 6. Comparison of TLR4 mRNA level among the five groups. The TLR4 mRNA level of the Dex1.5G and Dex4.5G was much lower than that of the MG (P<0.05). # meant P<0.05 when two groups were compared.

blood pressure, compensate for blood pressure decline and acidosis caused by endotoxins and improve visceral perfusion, showing good protective effects [24].

In conclusion, Dex has a protective effect on lung tissues in ALI rats. The higher dose resulted in a more significant protective effect on lung tissues. However, this study focused more on the pathological aspects, including only 3 doses. Therefore, the results may be biased and not representative enough. Future studies will be more extensive and in-depth, providing more effective methods for the treatment of ALI.

Acknowledgements

Medical and Health Science Technology Development Plan of Shandong Province: Study on the protective effect and mechanism of dexmedetomidine in endotoxin-induced lung injury (2017WSA18059).

Disclosure of conflict of interest

None.

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