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EFFECTS OF DEXMEDETOMIDINE ON SEPSIS INDUCED-LUNG INJURY AND CD54 EXPRESSION

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Received: 4 November 2021; **Accepted:** 10 December 2021

ABSTRACT

Sepsis is a systemic inflammatory response syndrome (SIRS) that occurs when the body's immunity overreacts to an infection. It is followed by life-threatening medical consequences, including multiple organ failure (MOD). Dexmedetomidine (DEX) is a selective 2 adrenergic agonist that is used as a short-term sedative in the ICU. Apart from improving sepsis prognosis, it is believed to have an organ protecting function. Our study aimed at confirming DEX ameliorative role in sepsis-induced organ damage. We also studied DEX mitigating effect on sepsis-induced acute lung injury (ALI) and elucidated the possible mechanism. Thirty rats were randomly assigned into three groups (n=10): sham, cecal ligation and puncture (CLP)-induced sepsis, or DEX-treated CLP (DEX + CLP). 15 minutes before the CLP procedure, a prophylactic dosage of DEX (5g/kg) was given intraperitoneally (IP). Animals were slaughtered 48 hours after the surgery was completed. Histological examination for tissue samples from lung, liver and kidney. CD54 expression in lung tissue was also investigated. Blood was also taken for hematological analysis. CLP rats showed different pathological lesions in lung, kidney and liver. We reported severe pulmonary tissue damage in CLP group accompanied with enhanced CD54 expression. DEX decreased the severity of histopathological changes in the affected organs and reduced the expression of CD54 in the lung tissue as well. However, DEX could not improve sepsis-induced hematological impairment. DEX attenuated sepsis through decreased CD54 expression in the lung as well as its hepato-renal protective effect in the CLP model.

List of abbreviations

AKI: acute kidney damage; ALI: acute lung injury; α7nAchRs: α7-nicotinic acetylcholine receptors; ARDS: acute respiratory distress syndrome; CLP: cecal ligation and puncture; DEX: Dexmedetomidine; ECs: endothelial cells; H& E: hematoxylin and eosin; H_2O_2: hydrogen peroxide; ICAM-1: intracellular cell adhesion molecule; IP: intraperitoneally; MOD: multiple organ failure; PBS: phosphate-buffered saline; PMNs: polymorphonuclear leukocytes; ROS: reactive oxygen species SC: subcutaneously; SIRS: systemic inflammatory response syndrome. VCAM-1: vascular cell adhesion molecule.

Keywords *:* Dexmedetomidine; Sepsis; Hematological picture; Histopathology; CD54.

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INTRODUCTION

Sepsis is a systemic, uncontrolled, large inflammatory reaction that can lead to septic shock or multi-organ failure, both of which can be fatal (Dellinger *et al.,* 2013; Kalil *et al.,* 2007). It is primarily mediated by interactions between invading pathogens and the host immune system, which results in a huge release of inflammatory mediators (Avlas *et al.,* 2011).

The pathogenesis of sepsis is thought to be characterized by endothelial dysfunction (Aird, 2003; Hack & Zeerleder, 2001). The production of vascular cell adhesion molecule (VCAM-1) and intracellular cell adhesion molecule (ICAM-1; CD54) is induced by inflammatory stimuli, proinflammatory cytokines, and bacterial components such as LPS (Osborn, 1990; Tsokos & Fehlauer, 2001). CD54 mediates polymorphonuclear leukocytes (PMNs) adhesion to endothelial cells (ECs) followed by their transmigration into the site of injury inducing an uncontrolled inflammatory response (Czermak *et al.,* 1999; Welty-Wolf *et al.,* 2001). Studies have reported a direct relation between plasma levels of CD54, number of organs damaged and mortality in human sepsis (Sessler *et al.,* 1995; Skibsted *et al.,* 2013).

The lung is the major critical organ that is most likely to be injured early in sepsis (Bone *et al.,* 1992). Sepsis-induced ALI is caused by an overactive inflammatory response mediated by CD54, which results in extensive endothelial and epithelial damage, which can proceed to acute respiratory distress syndrome (ARDS) in severe cases (Czermak *et al.,* 1999). One strategy for reducing ALI in sepsis is to limit the influx of PMNs into the lung tissue (Welty-Wolf *et al.,* 2001), thus modifying CD54 expression in pulmonary tissue could be of value in that respect.

Hepatorenal dysfunction is a key indication of sepsis and has a significant impact on sepsis patients' prognosis (Hutchins *et al.,* 2013; Vachharajani *et al.,* 2016; Yan *et al.,* 2014). It commonly occurs due to the sepsis induced massive inflammatory reactions and the associated oxidative stress induced damage as well (Hutchins *et al.,* 2013; Park *et al.,* 2012; Stewart *et al.,* 2005; Vachharajani *et al.,* 2016; Yan *et al.,* 2014).

Despite years of detailed research, sepsis treatment remains mostly supportive, with only a few medicines available to ease organ damage and prevent the patient's state from deteriorating (Dellinger *et al.,* 2013).

DEX is a selective α_2 adrenergic receptor and imidazoline receptor agonist (Zhang *et al.,* 2017). It's commonly utilized in ICUs because, unlike midazolam and propofol, it has a greater safety margin and can improve a patient's ability to tolerate pain through sedation (Kawazoe *et al.,* 2017). DEX has been studied to have immunomodulatory effect mediated through upregulation of α7-nicotinic acetylcholine receptors (α7nAchRs) and reduction of proinflammatory cytokines levels (Kong *et al.,* 2017).

Few studies have demonstrated the potential protective effect of DEX over single critical organ affection in sepsis as lung, liver or kidney (Jiang *et al.,* 2019). Its possible preventive impact against sepsis-induced multi-organ affection, however, has never been investigated. Debatable studies have also argued against DEX's role in organ protection in sepsis. Previous research has found no difference in liver and kidney safety outcomes between DEX-treated septic patients and non-DEX-treated septic patients (Pandharipande *et al.,* 2010). Hypotension and bradycardia associated with DEX administration can influence the hemodynamic stability of the septic patients as well (Scibelli *et al.,* 2017).

CLP is considered one of the widely studied murine animal models as it mimics human sepsis, thus, could be used beneficially in paving the way for new pharmacotherapy (Zhang *et al.,* 2015).

The aim of the current study is to confirm the possible ameliorative role of DEX over organs affection induced by sepsis in CLP rat model. We thought to further evaluate

the role of CD54 in sepsis-associated ALI and whether DEX can mitigate ALI through its modulation.

MATERIALS AND METHODS

1 - Animals and Experimental design

All procedures were carried out following the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996. All efforts were made to minimize the number of animals used and their suffering. Wistar albino adult female rats of 250–300 grams were allowed *ad libitum* access to food and water. They were kept in stainless steel cages in the Faculty of Medicine animal house at room temperature under a 12 hrs day-night cycle. A total of 30 rats were randomized into three groups (n= 10): sham, CLP and DEX + CLP groups. The details of each group treatment are summarized in (table 1). Sham group underwent laparotomy followed by scarification after 48 hrs. CLP group underwent CLP procedure followed by scarification after 48 hrs as well. DEX + CLP group received DEX (Sigma-Aldrich, USA) 5 μg/kg IP 15 min preoperative followed by the CLP procedure.

2 - The Constitution of Experimental Sepsis Model by Cecal Ligation and Puncture.

The skin on the abdomen was shaved and prepared with a 10% povidone-iodine solution. A 2 cm long midline laparotomy was performed. To avoid intestinal blockage, the cecum was exposed and ligated immediately distal to the ileocecal valve. The cecum was perforated with an 18-gauge needle, gently squeezed to extrude a little amount of excrement from the perforation sites into the typically sterile peritoneal cavity, and then returned to the abdominal cavity to induce sepsis. The abdominal cavity was closed in two layers. Sham-operated animals underwent the same surgical procedure, except the cecum was neither ligated nor punctured. All groups received normal saline subcutaneously (SC) (3 mL/100 g body weight) immediately after the surgical procedure to prevent dehydration (Zhang *et al.*, 2017).

3 - Hematological parameters:

Before scarification, blood samples were obtained into tubes containing anticoagulant for hematological analysis. An electronic blood cell counter was used to perform a hematological study (Veterinary Exigo Hematology analyzer, Sweden).

4 - Histopathological examination.

Fresh specimens from lung, liver and kidney of rats from all experimental groups were collected and fixed in 10% neutral buffered formalin. The tissues were dehydrated in a graded alcohol series, cleared with methyl benzoate, embedded in paraffin wax, sectioned at 4 µ thicknesses and stained with hematoxylin and eosin (H&E). Histopathological examination was done by light microscopy (Olympus CX31, Japan) and photographed using digital camera (Olympus, Camedia C-5060, Japan) (Suvarna *et al.*, 2018). Scoring of histopathological changes in lung, liver and kidney was examined according to (Sezer *et al.*, 2010; Gu *et al.*, 2016).

5 - Immunohistochemistry.

CD54 was detected using immunohisto-chemistry on paraffin slices from the lungs. The tissue sections were deparaffinized and hydrated before being washed with DW. Antigen retrieval took 20 minutes in a water bath with citrate buffer (pH 6). With 3 percent hydrogen peroxide (H_2O_2), the endogenous peroxidase activities were eliminated. The sections were then incubated for 1 hour at room temperature in a humidified chamber with a diluted polyclonal primary antibody (goat anti-rat CD54, company name, 1:200 dilution, Thermofisher Scientific Company). The staining was performed using Power-Stain the anti-goat HRP DAB Cell according to the manufacturer's instructions. Then sections were rinsed with phosphate-buffered saline (PBS) three times/5 min each and were incubated in anti-goat HRP Conjugate for 20 min at RT. A mixture of

DAB chromogen visualized the sections, and DAB substrate then incubated for 3 min. Sections were washed by DW, counterstained with hematoxylin (blue), dehydrated and mounted (Yamazaki *et al.*, 1993).

Statistical analysis:

The difference between the study groups was calculated and was found to be significant at p 0.05. The results were presented as a mean + standard deviation. The independent t-test was used to determine histopathological scoring. GraphPad Prism software version 7.04 was used to create the graphs.

RESULTS

1 - The hematological parameters in the study groups

When compared to the sham group, the CLP group had a substantial drop in WBCs, lymphocytes, monocytes, HGB, HCT, and RBCs, as indicated in table 1. The preceding hematological metrics did not differ significantly between the CLP and DEX + CLP groups. These findings revealed that DEX did not help the CLP group's hematological parameters exacerbated by sepsis.

2 - Histopathological changes of lung, liver and kidney in the study groups

***Lung*:** As shown in *Fig. 1*, lung tissues displayed severe catarrhal broncho-pneumonia and hyperplasia of peri-bronchial lymphocytic aggregation associated with congestion of some blood vessels in CLP group (Fig. 1A). Alveolar catarrhal pneumonia was very obvious in most cases detected as alveoli filled with mucin infiltrated with neutrophils and macrophage cells (Fig. 1B). DEX + CLP group's lung displayed hyperplasia of bronchial epithelium and moderate interstitial pneumonia (Fig. 1C). Compensatory emphysema was observed in most cases as well (Fig. 1D). Scoring of the histological findings in the lung sections are shown in (Fig. 2)

3- Liver: Hepatocyte vacuolar degeneration with substantial central venous congestion were the most common lesions seen in the CLP group (Fig. 3A). H&E revealed severe vacuolar degeneration as distinct vacuoles (Fig. 3B). A moderate amount of inflammatory cells were also collected (Fig. 3C). The DEX + CLP group had considerable central venous congestion and hepatocyte vacuolar degeneration was reduced (Fig. 3D). Figure 5 depicts the histological findings in liver sections.

Kidney: CLP group's kidney showed very remarkable changes. They were expressed by congestion of glomerular capillaries obliterating bowman's space and formation of fibrin thrombi in the other glomerular capillaries associated with vacuolar degeneration in renal epithelium (Fig. 4A). Some cases showed focal necrosis and desquamation of the renal epithelium with loss of brush border in renal tubules associated with interstitial hemorrhage (Fig. 4B). The appearance of hyaline casts in the lumen of some renal tubules was also observed (Fig. 4C). DEX + CLP group's kidneys showed congestion of some glomerular capillaries with diminution in renal epithelial damage (Fig. 4D). The histological findings in the kidney sections are presented in (Fig. 5).

4 - CD54 expression of the lung in the study groups

CD54 is a low-expression surface antigen found in the pulmonary endothelium, lymphocytes, neutrophils, and macrophages (Fig. 6A). CD54 was found to have a high level of expression in the pulmonary microcirculation in the ECs of alveolar capillaries, as well as upregulation in the CLP group's lung tissue (Fig. 6B). The DEX + CLP group, on the other hand, revealed just a mild expression in alveolar capillaries (Fig. 6C). These findings showed that DEX treatment reduced CD54 expression in lung tissue and the related pulmonary microcirculation, implying that DEX can help with CLP-induced ALI.

Table 1: The hematological parameters in the study groups.

	Sham Mean ± SD	**CLP** Mean ± SD	*** P-value**	**DEX + CLP** Mean ± SD	****P-value**
WBC (x109/L)	9.73 ± 2.59	5.95 ± 2.55	0.05	5.00 ± 2.55	0.71
LYM (x109/L)	4.97 ± 2.01	2.50 ± 1.51	0.04	1.35 ± 0.92	0.32
MONO (x109/L)	1.01 ± 0.30	0.38 ± 0.31	0.02	0.05 ± 0.07	0.13
NEUTRO (x109/L)	2.63 ± 1.69	2.40 ± 1.53	0.81	3.10 ± 1.13	0.57
EOS (x109/L)	1.28 ± 0.55	0.68 ± 0.69	0.18	0.50 ± 0.42	0.72
HGB (gm/dl)	13.30 ± 1.04	10.07 ± 0.38	0.00	15.00 ± 1.41	0.11
HCT (%)	37.31 ± 3.56	28. ± 1.16	0.00	41.40 ± 4.10	0.13
RBC (106/µL)	7.26 ± 0.89	5.31 ± 0.29	0.00	7.62 ± 0.70	0.11
MCV (fl)	53.20 ± 3.44	53.55 ± 1.24	0.78	54.35 ± 0.35	0.30
MCH (pg)	18.80 ± 1.24	19.33 ± 0.40	0.25	19.65 ± 0.07	0.31
MCHC (gm/dl)	35.58 ± 0.60	35.93 ± 0.35	0.25	36.20 ± 0.14	0.33
RDW (%)	20.44 ± 0.86	20.15 ± 1.15	0.67	20.35 ± 1.48	0.89
PLT (109 /L)	994.45 ± 241.59	630.50 ± 92.37	0.00	731.00 ± 90.51	0.32
MPV (fl)	6.70 ± 0.38	6.58 ± 0.87	0.80	7.30 ± 0.42	0.24

* Independent t-test: Sham x CLP.
** Independent t-test: CLP x DEX + CLP.

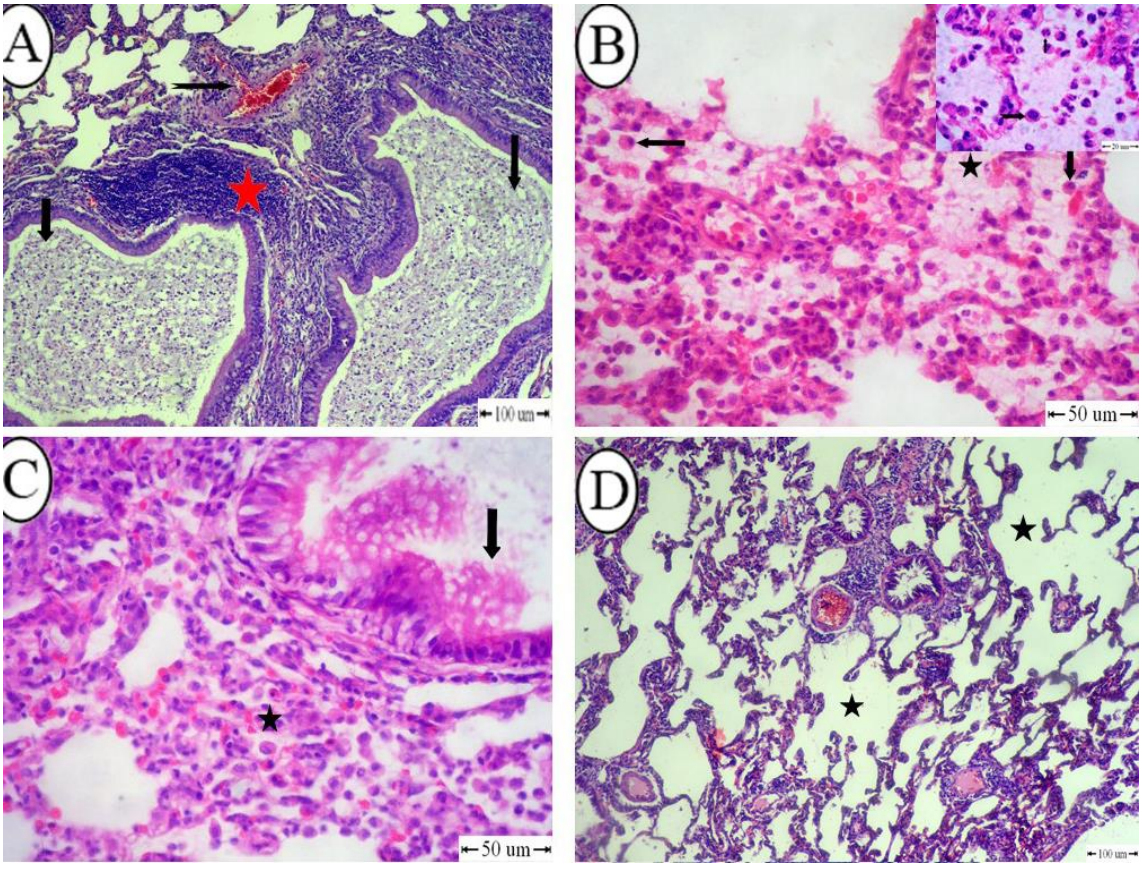

Fig. 1: Lung histopathology in CLP & DEX + CLP groups. CLP lung **(A)** showing severe catarrhal bronchopneumonia (arrow), hyperplasia of peri-bronchial lymphocytic aggregation (star) and congestion of some blood vessels (notched arrow). H&E. bar=100, **(B)** Showing alveolar catarrhal pneumonia (arrow). bar=50. Higher magnification in the Sho insert showed Alveoli filled with mucin (star), infiltrated with neutrophils (arrow) and macrophage cells (notched arrow). bar=20. H&E. DEX + CLP lung **(C)** showing hyperplasia of bronchial epithelium (arrow) and moderate interstitial pneumonia (star). H&E. bar=50. **(D)** Showing compensatory emphysema (star). bar=100. H&E.

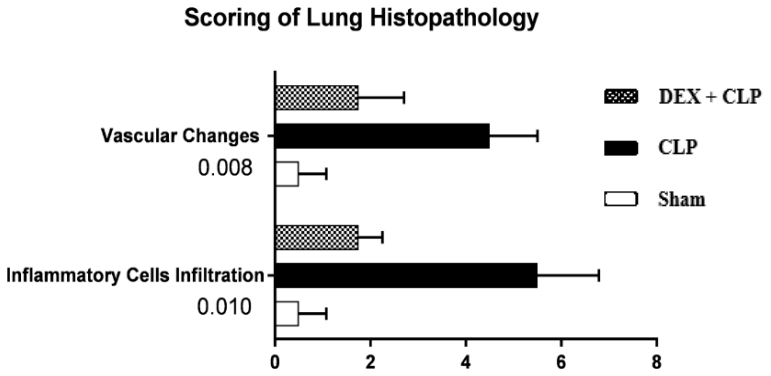

Fig. 2: Histopathological scoring of the lung in the study groups. To grade the extent of lung inflammation, semiquatitative scoring system was used. Briefly, to score the inflammatory cell infiltration, cell counts were performed blind based on five points grading system for the following features: 0: normal, 1: few cells, 2: a ring of inflammatory cells 1 cell layer deep; 3: a ring of inflammatory cells 2–4 cells deep, 4: a ring of inflammatory cells of, > 4 cells deep. Five fields were counted for each slide. Vascular changes were detected in all experimental animals according to the grading system as follow: 0: normal, 1: Congestion of blood vessels, 2-4: Thrombosis of blood vessels, >4 hemorrhage. n=10.

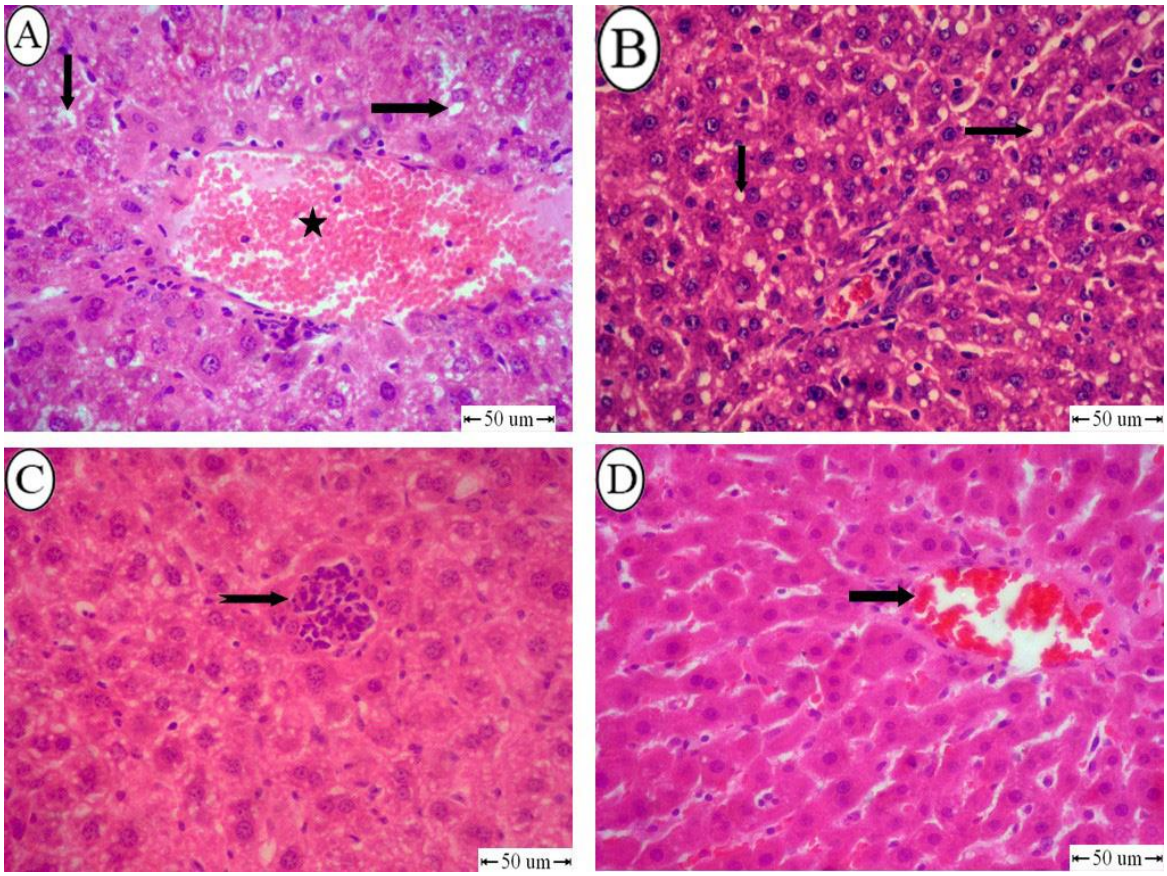

Fig. 3: Histopathological changes of the liver in the CLP & DEX + CLP groups. CLP group **(A)** showing vacuolar degeneration (arrow) and severe congestion of central vein (star), **(B)** showing vacuolar degeneration (arrow), **(C)** showing focal of inflammatory cells. DEX + CLP **(D)** group showing moderate congestion of central vein (arrow), note disappearance of vacuolar degeneration in hepatocytes. H&E. bar=50.

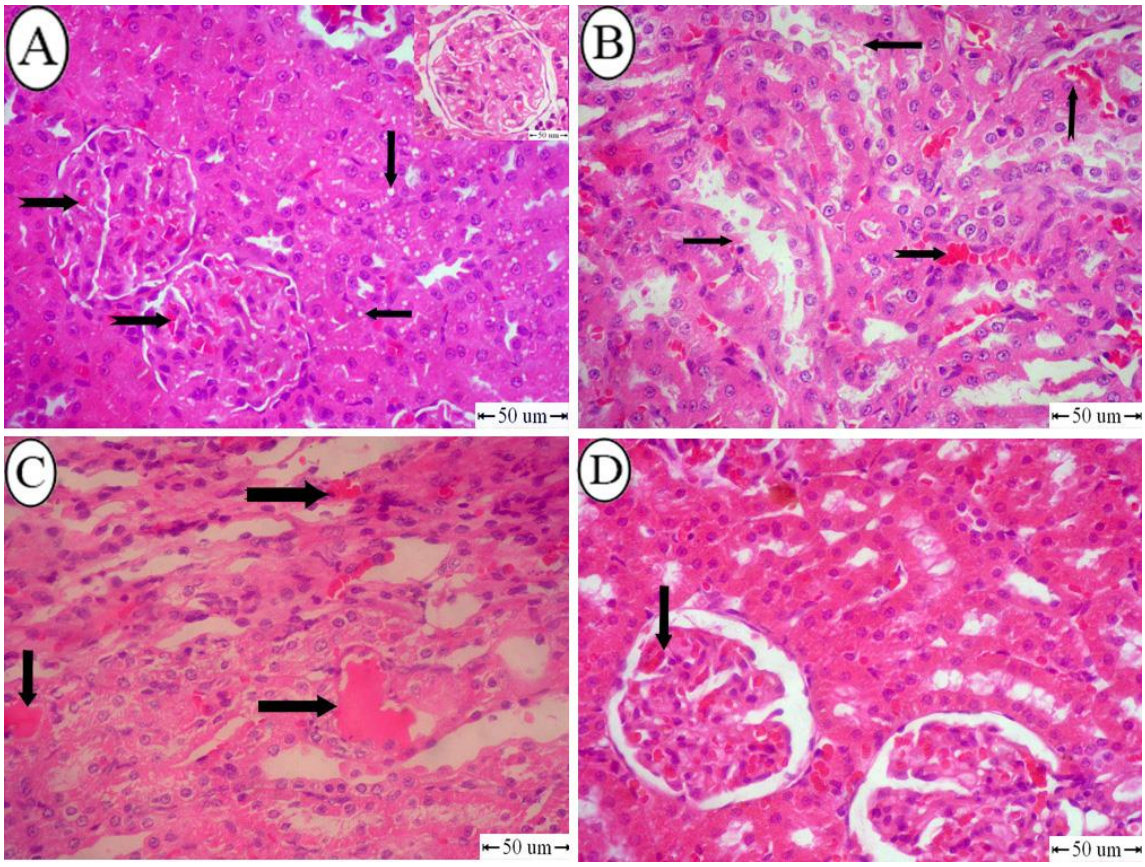

Fig. 4: Histopathological changes of the kidney in CLP & DEX + CLP groups. CLP group **(A)** showing congestion of glomerular capillary (notched arrow) and mild vacuolar degeneration in renal epithelium (arrow) associated with glomerular fibrin thrombi in the insert, **(B)** showing focal necrosis and desquamation of the renal tubular cells (arrow) and interstitial hemorrhage (notched arrow), **(C)** showing renal intratubular hyaline casts (arrow). DEX+CLP group **(D)** showing congestion of glomerular capillary (arrow). H&E. bar =50.

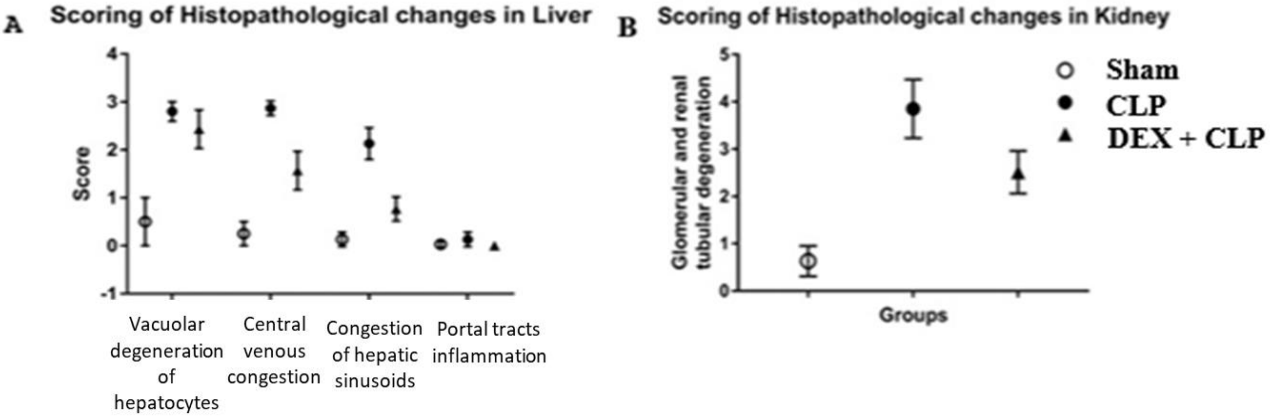

Fig. 5: Histopathological scoring of the liver and the kidney in the study groups. (A) Histopathology scoring of hepatic lesions showed significant decrease in vacuolar degeneration of hepatocytes, congestion of central vein and congestion of hepatic sinusoids in DEX + CLP group compared to CLP group. **(B)** Histopathology scoring of renal lesions showed significant decrease in renal glomerular degeneration and renal tubule necrosis in DEX + CLP group compared to CLP group. n=10.

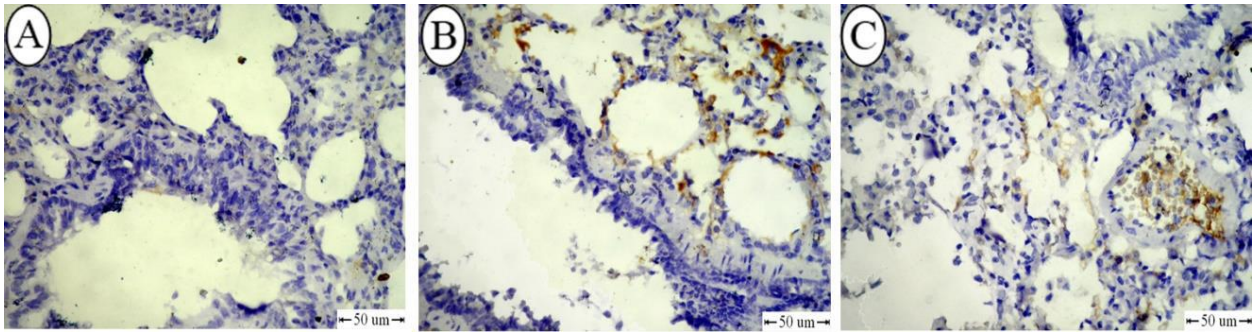

Fig. 6: CD54 expression in the lung of the study groups. (A) Sham, showing normal lung ECs of alveolar capillaries not stained **(B)** CLP, showing lung tissue stained for CD54 with strong expression in ECs of alveolar capillaries **(C)** DEX + CLP, revealing a faint expression of CD54 in alveolar capillaries. bar=50.

DISCUSSION

In this study, we used the CLP rat model, which is a commonly used sepsis model to confirm the potential therapeutic benefits of DEX in sepsis. In comparison to the sham group, sepsis was established through histopathological and hematological investigation. In CLP rat models, we highlighted the potential beneficial effects of DEX on hepatorenal diseases produced by sepsis. For the first time, we demonstrated that DEX effectively reduced CLP-induced ALI by lowering CD54 expression, a hallmark of endothelial activation and organ damage caused by sepsis. As a result, it was able to attenuate the inflammatory cascade in injured lung tissue endothelia.

Sepsis is a massive inflammatory response that may proceed into refractory immunosuppression and life-threatening organ dysfunction (Hotchkiss *et al.*, 2013b). Previous literature confirmed that sepsis therapy should not be limited to antimicrobial treatment as correcting the dysregulated immune response is mandatory (Hotchkiss *et al.*, 2013a).

Recently, it has been found that the cholinergic system has an in vivo immune regulatory action through its anti-inflammatory effect (Borovikova *et al.*, 2000). Thus, sympatholytic agents as α_2 adrenergic agonist drugs can have a role in alleviating massive inflammatory response in sepsis through shifting the balance towards the cholinergic action (Liu *et al.*, 2016).

DEX is a popular sympatholytic drug in the ICU because it gives a unique conscious sedation without respiratory depression, making endotracheal intubation and other invasive operations easier (Venn *et al.*, 1999). DEX's activity is mediated by its agonistic action on 2 adrenergic receptors and imidazoline receptors (Zhang *et al.*, 2017). DEX-mediated hyperpolarization of noradrenergic neurons suppresses norepinephrine (NE) release and sympathetic outflow, which causes the sedative effect (Kaur & Singh, 2011). DEX opens up new possibilities for immunomodulation (Wakabayashi *et al.*, 1991) as it exerts potential anti-inflammatory effect, decreases the levels of inflammatory cytokines in endotoxemic rodents and increasing their survival rate (Qiao *et al.*, 2009; Ma *et al.*, 2018; Yun *et al.*, 2017).

Animal models of sepsis are thought to be useful and inexpensive research tools. The CLP model is the gold standard in sepsis research because it is the most consistent with human sepsis clinical outcomes (Zhang *et al.*, 2015). The cecum is ligated, which causes ischemia and supplies a source of ischemic tissue. Bowel perforation, on the other hand, causes

excrement flow into the peritoneum and bacterial peritonitis. The CLP model also mimics the pathophysiologic, hemodynamic, and criteria of cytokine- and chemokine-mediated immune dysfunction seen in clinical sepsis (Wichterman *et al.*, 1980). It shows the phenotypes of multiple organ dysfunction as well (Li *et al.*, 2018).

In our study, CLP group showed a significant decrease in WBCs, lymphocytes, monocytes, HGB, HCT and RBCs when compared with the sham group. According to Hotchkiss *et al.*, 1997, the WBC drops intensely shortly after septic challenge as a result of lymphocyte apoptosis. Leukopenia carries a bad prognosis compared to leukocytosis in severe sepsis patients (Molnar *et al.*, 2015). The noteworthy reason for the lower RBCs count in the CLP group was bone marrow suppression in sepsis and blood hemolysis generated by the rapid increase in RBC sphericity, decreased deformability, and thus destruction (Goyette *et al.*, 2004).

There was no significant change in blood values between the CLP and DEX + CLP groups in this investigation, indicating that DEX had no effect on sepsis-related blood parameters. The lower Hb and PCV could be explained by the merging of circulatory blood cells in the spleen or other reservoirs as a result of diminished sympathetic activity (Verma *et al.*, 2018).

The pathophysiological process of sepsis is a sequel of uncontrolled overproduction of inflammatory cytokines, cytokine storm (Chaudhry *et al.*, 2013), mediated through NF-κB, STAT3, and MAPKs signaling mechanisms (Hosoi *et al.*, 2004; Shimamoto *et al.*, 2006). After its activation, NF-κB is translocated from the cytoplasm to the nucleus and initiates downstream gene transcription of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6) (Huang & Hung, 2013). TNF-α and IL-1β can stimulate inflammatory cascades that produce reactive oxygen species (ROS) causing organ injuries especially in liver (Wichmann *et al.*, 1996; Cohen, 2002; Han *et al.*, 2017; Ji *et al.*, 2018).

The lung is the primary organ to which inflammatory mediators generated and released throughout the sepsis process are directed (Aird, 2003). Over 40% of people with sepsis develop ALI, which lowers the patient's prognosis (Iscimen *et al.*, 2008). The endothelium's general malfunction is a critical event in the development of sepsis (Aird, 2003; Hack & Zeerleder, 2001). When the endothelium becomes active during sepsis, it converts into a procoagulant, antifibrinolytic, and pro-adhesive state, which is driven primarily by complement activation (Ait-Oufella *et al.*, 2010). (Riedemann *et al.*, 2002). C5a directly activates ECs causing upregulation of cellular adhesion molecules E-selectin, VCAM-1 and ICAM-1 (CD54) (Riedemann *et al.*, 2002). CD54 is a cell-surface protein that is expressed at very low levels on pulmonary endothelium (Welty-Wolf *et al.*, 2001). The expression is upregulated during septic processes after stimulation by inflammatory mediators as cytokines and bacterial lipopolysaccharides (Osborn, 1990; Tsokos & Fehlauer, 2001). CD54 mediates inflammatory responses via adhesion of leukocytes to activated endothelium and subsequent leukocyte transmigration through the pulmonary endothelial layer (Osborn, 1990; Meerschaert & Furie, 1995; Lukacs, 1996).

CD54 deficiency has been demonstrated to have a positive impact in some studies, suggesting that targeting the CD54 pathway could be a viable therapy strategy for ALI/ARDS patients (Svedova *et al.*, 2017; Van Griensven *et al.*, 2006). Others, on the other hand, found that blocking it affects survival in septic animals (Welty-Wolf *et al.*, 2001; Svedova *et al.*, 2017). The availability of multiple models, according to Van Griensven *et al.*, 2006, could be the cause of the inconsistent results.

Inflammatory cytokines have been shown to dysregulate the immune response, driving the dynamic process of sepsis and resulting in multi-organ affection (Schulte *et al.,* 2013; Wu *et al.,* 2013). In sepsis, the liver plays an important role in removing infectious pathogens, adjusting metabolism, and producing acute-phase reactant proteins and cytokines (Savio *et al.,* 2017; Yan *et al.,* 2014; Yang *et al.,* 2019). Liver has a critical role in sepsis as getting rid of infectious agents, adapting metabolism and manufacturing acute-phase reactant proteins and cytokines (Hutchins *et al.,* 2013). The most prominent lesions found in the liver of the CLP group were vacuolar degeneration with significant congestion of the central vein and hepatic sinusoids, according to histopathological investigation. DEX reduced vascular alterations and inflammation in the portal tracts, preventing liver damage in endotoxemia (Sezer *et al.,* 2010). DEX was also found to minimize the histological alterations of hepatic ischemia damage in rats when given prior to the surgery, but had no impact when given after the procedure (Chen *et al.,* 2017).

In the present study, a significant decrease in the most histopathological lesions in the liver of CLP group was observed in DEX group, probably, due to the inhibitory effect of DEX on cytokine responses to endotoxemia.

In serious instances, sepsis is the most common cause of acute kidney damage (AKI) (Ma *et al.,* 2019). In contrast to renal-ischemia reperfusion, which is usually associated with irreversible damage, sepsis-induced AKI is characterized by reversible harm of the renal tubular epithelial cells (Payen *et al.,* 2012; Ma *et al.,* 2019). The levels of the cytokines IL-6, IL-10, and macrophage migration inhibitory factor have been linked to the development of sepsis-induced AKI (Payen *et al.,* 2012). The amplified inflammatory signal induces circulatory impairment with maldistribution of tissue blood flow (Donati *et al.,* 2013). Sepsis induced-ECs injury produces less release of vasodilators (e.g. nitric oxide, NO) with more enhanced response to vasoconstrictors with further redistribution of blood flow and further renal injury (Ma *et al.,* 2019).

The CLP group's kidneys showed vascular abnormalities, including a decrease in Bowman's space and vacuolar degeneration in the renal epithelium. Experimentally generated septicemia in buffalo calves yielded similar outcomes (Annas *et al.,* 2014). Glomerular damage and renal epithelial degeneration were considerably reduced in the DEX + CLP group. DEX has been shown in previous trials to reduce the histopathologic damage associated with renal ischemia and to improve kidney tolerance (Wijeysundera *et al.,* 2003).

CONCLUSION

Our current study provides significant evidence of the potential benefit of DEX for treating critically ill septic patients. Our findings delineated the role of DEX in attenuating multiple organ dysfunctions that will certainly improve the outcome of sepsis without ameliorating hematological impairment. DEX was, basically, studied to mitigate sepsis induced ALI through down regulating CD54 expression, up-regulated in the CLP group.

LIMITATIONS

Our study has some limitations. First, CLP rats, in fact, imitated mainly the peritonitis process; thus, the results can't equate with human sepsis. Second, we used only single preemptive dose of DEX that may be responsible for the slight improvement in organ histopathology induced by sepsis. Repeated doses of DEX or DEX infusion may give better ameliorative effect. Third, fluid resuscitation and norepinephrine infusion are commonly used in human sepsis, however, we did not try in combination with DEX in our study. Their

combined administration with DEX may give better synergistic effect compared with DEX treatment as a sole agent.

COMPETING INTEREST

The authors have declared that no competing interests exist.

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تأثير ديكسميديتوميدين على إصابة الرئة الناتجة عن الإنتان وتعبير سي دي 54

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يعد الإنتان هو متلازمة الاستجابة الإلتهابية الجهازية التي تسببها استجابة الجسم للعدوي. عادة ما يكون مصحوبًا بمضاعفات طبية خطيرة، لا سيما اختلال وظائف الأعضاء المتعددة. ديكسميديتوميدين هو ناهض أدرينالي الفا2 انتقائي يستخدم كمسكن قصير الأمد في وحدة العناية المركزة. يقال أن له تأثير وقائي للأعضاء إلى جانب تحسين تشخيص الإنتان. تهدف دراستنا إلى تأكيد الدور التحسني لـ ديكسميديتوميدين في تلف الأعضاء الناجم عن تعفن الدم. درسنا أيضًا تأثير ديكسميديتوميدين المخفف على إصابة الرئة الحادة التي يسببها الإنتان وشرحنا الآلية الكامنة المحتملة. تم اختيار ثلاثين جرذاً عشوائياً قسمت إلى ثلاث مجموعات (عدد المجموعه = 10) : المجموعه الضابطة ومجموعة تعفن الدم عن طريق ربط وثقب الأعور ومجموعة تعفن الدم عن طريق ربط وثقب الأعور المعالجة بـ ديكسميديتوميدين. أعطيت جرعة وقائية من ديكسميديتوميدين (5 ميكروغرام/ كغ) داخل الصفاق قبل 15 دقيقة من إجراء ربط وثقب الأعور. تم ذبح بالحيوانات بعد 48 ساعة من الإجراء. تم جمع عينات الأنسجة من الرئة والكبد والكلى لفحص الباثولوجي للأنسجة ودراسة تعبير سي دي 54 في أنسجة الرئة. تم جمع الدم أيضًا من أجل دراسة تحليل الدم. أظهرت فئران مجموعة تعفن الدم عن طريق ربط وثقب الأعور آفات مرضية مختلفة في الرئة والكلى والكبد. لقد رصدنا تلف شديد في الأنسجة الرئوية في مجموعة تعفن الدم عن طريق ربط وثقب الأعور مصحوبًا بتحسن في تعبير سي دي54 .قلل ديكسميديتوميدين من شدة التغيرات النسيجية المرضية في الأعضاء المصابة كما قلل ديكسميديتوميدين أيضا من تعبير سي دي54 في أنسجة الرئة. ومع ذلك ، لا يمكن أن يحسن ديكسميديتوميدين التغيرات في الدم الناتجه عن الإنتان. يخفف ديكسميديتوميدين من تعفن الدم من خلال تنظيم تعبير سي دي54 في الرئة بالإضافة إلى تأثيره الوقائي علي الكبد والكلي في نموذج تعفن الدم عن طريق ربط وثقب الأعور .

الكلمات الدالة

ديكسميديتوميدين. تعفن الدم. صورة الدم. هستوباثولوجي. سي دي54.