

## ORIGINAL ARTICLE

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**Dexmedetomidine improves ultrastructural view of renal damage and biochemical parameters during an experimental inflammatory bowel disease**Gulay Erdogan Kayhan<sup>1</sup>, Basak Kayhan<sup>2</sup>, Mehmet Gul<sup>3</sup>, Zeynal Mete Karaca<sup>4</sup><sup>1</sup>*Osmangazi University, Faculty of Medicine, Department of Anesthesia and Reanimation, Eskişehir, Turkey*<sup>2</sup>*Inonu University, Institute of Liver Transplantation, Malatya, Turkey*<sup>3</sup>*Inonu University, Faculty of Medicine, Department of Histology and Embryology, Malatya, Turkey*<sup>4</sup>*Inonu University, Faculty of Medicine, Department of Medical Biology and Genetics, Malatya, Turkey*

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**Abstract**

Investigation of the effect of Dexmedetomidine (Dex) on inflammatory bowel diseases (IBD) induced renal damage by using an experimental model. IBD frequently cause reduction in renal function and renal failure. Since perioperative anesthesia and postoperative conditions in intensive care can cause acute kidney injury and reduction on renal function; deciding on a sedative and anesthetic agent without side effects would reduce IBD caused renal damage. We investigated histopathological, electron microscopic analyzes and antioxidant effects of Dex on kidney tissue during trinitrobenzene sulfonic acid (TNBS) induced damage in BALB/c mice at two different concentrations of Dex; 5µg/kg and 30µg/kg. Blood samples were collected to analyze creatinine levels. The levels of malondialdehyde (MDA) and activity of antioxidant enzymes glutathione (GSH) and superoxide dismutase (SOD) were measured in tissue homogenates. Histopathological and ultrastructural changes in kidney following TNBS induction were significantly reduced in Dex treatment groups. Administration of Dex significantly reduced creatinine levels. MDA levels were significantly reduced in Dex groups. Administration of Dex brought back GSH level to control level. Administration of Dex significantly 1.48 and 1.96 times increased SOD activity at 5µg/kg and 30 µg/kg, respectively. Dexmedetomidine treatment may have benefits to prevent IBD induced renal damage.

**Keywords:** Dexmedetomidine, Inflammatory Bowel Diseases, Renal Damage**Introduction**

Inflammatory bowel diseases (IBD), known as ulcerative colitis and Crohn's disease, are in a group of chronic inflammatory disease characterized as disabilities in gastrointestinal system accompanied by defective mucosal immune response [1,2]. Currently, the etiology of IBD is unknown however, that group of disease is classified according to several distinct factors such as hereditary and environmental factors, histopathological views, host immune response, and the location of inflammation in gastrointestinal system [3-5]. Besides that, extraintestinal manifestations and complications are common in patients with IBD and can involve almost any organ or system. Renal or urinary complications occur in 4-23% of patients, often in those with severe long-standing disease. Glomerulonephritis, amyloidosis, tubulointerstitial abnormalities, renal hypertension, pyonephrosis and pyelonephritis are the most seen renal complications in IBD. Since delay on detection of renal damage causes reduction on renal function and finally end stage renal failure, it is important to use convenient analgesics in intensive care units for those patients [6,7].

Dexmedetomidine is a highly specific, potent, and selective  $\alpha_2$ -adrenoceptor agonist. It is used to provide sedation and analgesia in patients receiving mechanical ventilation, in the form of infusions that do not exceed 24 h. application. Sedative, analgesic, and hypotensive effects of dexmedetomidine make it a valuable adjuvant during the perioperative period. As an  $\alpha_2$  adrenoceptor agonist, its interaction with its receptors in the nervous system abolishes the secretion of catecholamines in patients under stress [8,9]. Also, it has been shown that dexmedetomidine can also be used safely as a sedative agent during colonoscopy [10]. Dexmedetomidine suppresses proinflammatory cytokines, which are a part of the innate immune response in sepsis patients [11]. Furthermore, in our laboratory we have recently shown that dexmedetomidine down-regulates inflammatory response by inducing on Th2 and Th17 cytokine network [12].

Since perioperative anesthesia, medications, and postoperative conditions in intensive care can cause acute kidney injury and decrease on renal function [13-16], deciding on less toxic sedatives and anesthetic agents to use not only would prevent acute renal failure but also would reduce IBD caused renal damage in those patients. Thus; in this study; we investigated the effect of dexmedetomidine on renal histology and biochemical parameters to assess the level of damage caused by an experimental model of colitis; TNBS induced colitis.

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## Material and Methods

### Animals

Forty-eight males, 5-6 week old BALB/c mice ad libitum were housed in individual cages for 6 days in a well ventilated room with a 12:12-h light/dark cycle at 21°C. The experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals adopted by Animal Breeding and Care Center of Inonu University (Ethic No: 2016/A-42).

### Experimental Protocol

Animals were randomly divided into 6 groups, each of them consisting 8 mice. Accordingly;

- (I) Control group: mice received normal saline intraperitoneally (i.p)
- (II) TNBS- group: TNBS colitis was induced by administration of 150 µl TNBS-ethanol (50%w/v) intrarectally, as mentioned before (14),
- (III) TNBS+Dex (5 µg/kg) group: 5 µg/kg Dexmedetomidine was administered via i.p. following induction of colitis;
- (IV) TNBS+Dex (30 µg/kg) group: 30 µg/kg Dexmedetomidine was administered via i.p. following induction of colitis;
- (V) Dex5 group: 5 µg/kg Dexmedetomidine was administered via i.p.
- (VI) Dex30 group: 30 µg/kg Dexmedetomidine was administered via i.p.

Mice were anesthetized with ketamine/xylazine at 17.5mg/mL/2.5mg/mL in 0.1 mL volume during TNBS administration via intraperitoneally. After induction of colitis dexmedetomidine administration at two different concentrations were performed for 6 days. At last day of experiment (6<sup>th</sup> day) animals were sacrificed after ketamine/xylazine anesthesia and cardiac puncture to collect blood samples and tissue specimens were collected.

### Microscopic Examination

Mice in all groups were sacrificed after ketamine anesthesia at the end of the experiment. Kidney tissues were rapidly removed. Tissue samples were separated for histopathologic, ultrastructural and biochemical examinations. Each kidney sample was processed for light microscopic examination. The first portions were placed in 10% neutral buffered formalin for 48h and prepared for routine paraffin embedding. Sections of tissues were cut at 6 µm, mounted on slides, stained with hematoxylin-eosin (H&E). Periodic acid-Schiff (PAS) staining has been performed to examine glomerular and tubular basal membrane structure. Sections were examined by a Leica DFC280 light microscope and Leica Q Win and Image Analysis system (Leica Micros Imaging Solutions, Cambridge, UK) by a blind observer.

For electron microscopic evaluation, the kidney samples were fixed in 2.5% glutaraldehyde for 3 h buffered with 0.1 M NaH<sub>2</sub>PO<sub>4</sub> + NaHPO<sub>4</sub> (pH 7.2–7.4), postfixed in 1% osmium tetroxide (OsO<sub>4</sub>) for 2 h and embedded in Araldite CY 212. Ultrathin sections (80 nm) were contrasted with uranyl acetate and lead citrate and examined with Zeiss Libra 120 (Carl Zeiss NTS GmbH, Oberkochen, Germany) transmission electron microscope.

### Histopathological Scoring

Histopathological kidney damage was scored by grading glomerular, tubular, and interstitial changes with a maximum score of 27. Total score for each group has been divided into three to get average score.

Glomerular damage (sclerotic changes such as matrix expansion, narrowing or disappearance of the Bowman's space, capillary collapse, intraglomerular infiltration) was evaluated as 0, absent; 1, <25% of glomeruli affected; 2, 25–50% of glomeruli affected; 3, >50% of glomeruli affected.

Tubular injury was defined as tubular atrophy, epithelial degeneration. Grading for each of these tubular changes was scaled as 0, absent; 1, <25% of tubules affected; 2, 25–50% of tubules affected; 3, >50% of tubules affected. The presence of interstitial cell infiltration congestion and edema were each judged as 0, absent; 1, mild; 2, moderate; 3, severe. Thus; during worst damage in all criteria the total average score is 9.

The mean diameter of the glomeruli was determined by measuring the dimension of 100 glomeruli per section of all groups.

### Sample Preparation and Biochemical Analysis

The other parts of tissue samples were stored at –80°C for the determination of malondialdehyde (MDA), total glutathione (GSH) and superoxide dismutase (SOD). Tissues were homogenized (PCV Kinematica Status Homogenizator) in ice-cold phosphate buffered saline (pH 7.4). The homogenate was sonicated with an ultrasonifier (Bronson sonifier 450) by 3 cycles (20-s sonications and 40-s pause on ice). The homogenate was centrifuged (15.000g 10 min, 4°C) and cell-free supernatant was subjected to enzyme assay immediately.

Blood samples were obtained by cardiac puncture of anesthetized mice and centrifuged at 2500 g for 10 minutes to collect serum samples for analysis of creatinin levels. Serum creatinin levels were analyzed in an automated system (Abbot Architect C8000) according to manufacturer's instructions.

### Malondialdehyde (MDA) Assay

In order to analyze lipid peroxidation; a reaction mixture was prepared by adding 250 µL homogenate into 2 mL reaction solution (15% trichloroacetic acid: 0.375% 2-thiobarbituric acid: 0.25 N HCl, 1:1:1, w/v) and heated at 100°C for 15 min. The mixture was cooled to room temperature, centrifuged (10.000g for 10 min) and the absorbance of the supernatant was recorded at 532 nm. 1,1,3,3-tetramethoxypropane was used as MDA standard. MDA results were expressed as nmole/mg protein in the homogenate.

### Glutathione (GSH) Assay

The reaction mixture contained 50 mM sodium phosphate, 1 mM EDTA, 0.5 mM DTNB, 0.2 mM NADPH and 0.5 U/mL of glutathione reductase added on homogenate (10 µL) to initiate the reaction but was omitted for control. The formation of 5-thio-2-nitrobenzoate (TNB) is followed spectrophotometrically at 412 nm. The amount of GSH in the extract was determined as nmole/mg protein utilizing a commercial GSH as the standard.

### Superoxide Dismutase (SOD) Assay

SOD (Cu, Zn-SOD) activity in the supernatant fraction was measured using xanthine oxidase/cytochrome c method where 1 unit (U) of activity is the amount of enzyme needed to cause half-maximal inhibition of cytochrome c reduction. The amount of SOD in the extract was determined as U of enzyme mg<sup>-1</sup> protein, utilizing a commercial SOD as the standard.

### Statistical Analysis

Statistical evaluations were performed by SPSS for Windows version 13.0 (SPSS, Chicago, U.S.A.). All data were reported as means  $\pm$  standard error (SE). The distribution of data was determined by the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was performed in the analysis of quantitative data, and Tukey's test was used in sub analysis. Analysis with P value <0.05 was considered as statistically significant.

## Results

### Histological Analysis

According to histological examinations of H&E and PAS staining's, we observed that TNBS administration causes an inflammation in renal tissue. Administration of dexmedetomidine

significantly reduced histopathological scores of renal tissues during TNBS induced colitis Table 1. The kidney sections of naïve control (Figure 1A, B), Dex5 (Figure 2A, B) and Dex30 (Figure 2C, D) groups were assessed as normal kidney histology.

The most prominent changes observed in kidney sections of TNBS group. Narrowing of Bowman's space, intra-glomerular infiltration in glomerulus, atrophy in tubules and cell infiltration together with edema were prominent in TNBS induced group (Figure 1C, 1D).

Histopathological kidney damage was significantly reduced in dexmedetomidine administered groups (TNBS+Dex5 and TNBS+Dex30) in comparison to TNBS group (Table 1). That reduction reached to 3 times in TNBS+Dex5 (Figure 1E, 1F) and 4.42 times TNBS+Dex30 (Figure 1G, 1H) in total score. Nevertheless, mild tubular and interstitial changes and rarely glomerular changes were observed in dexmedetomidine administered TNBS group. There were no significant differences on recovering of kidney damage between two different doses of dexmedetomidine administration. Within all criteria only glomerular sclerosis formation was significantly reduced in TNBS+Dex30 group in comparison to TNBS+Dex5 group (Table 1).

**Table 1.** Histological scores of each group to evaluate the damage in renal tissues

| Group                    | Glomerular Damage   |                             |                    |                    | Tubular Damage     |                    | Interstitial Damage |                    |                    | Score               |
|--------------------------|---------------------|-----------------------------|--------------------|--------------------|--------------------|--------------------|---------------------|--------------------|--------------------|---------------------|
|                          | Sclerosis           | Narrowing of Bowman's Space | Collapse           | Infiltration       | Atrophy            | Degeneration       | Cell Infiltration   | Congestion         | Edema              |                     |
| Control                  | 0.00<br>$\pm 0.00$  | 0.00<br>$\pm 0.00$          | 0.00<br>$\pm 0.00$ | 0.14<br>$\pm 0.34$ | 0.00<br>$\pm 0.00$ | 0.00<br>$\pm 0.00$ | 0.14<br>$\pm 0.34$  | 0.00<br>$\pm 0.00$ | 0.00<br>$\pm 0.00$ | 0.03<br>$\pm 0.06$  |
| TNBS                     | 4.28<br>$\pm 1.15$  | 4.57<br>$\pm 1.17$          | 4.42<br>$\pm 1.17$ | 4.57<br>$\pm 1.17$ | 4.57<br>$\pm 1.17$ | 4.42<br>$\pm 1.17$ | 4.57<br>$\pm 1.17$  | 4.28<br>$\pm 1.15$ | 4.57<br>$\pm 1.17$ | *4.47<br>$\pm 0.12$ |
| TNBS+Dex5 5 $\mu$ g/kg   | #1.57<br>$\pm 0.49$ | 1.28<br>$\pm 0.45$          | 1.57<br>$\pm 0.49$ | 1.42<br>$\pm 0.49$ | 1.42<br>$\pm 0.49$ | 1.57<br>$\pm 0.49$ | 1.57<br>$\pm 0.49$  | 1.57<br>$\pm 0.49$ | 1.42<br>$\pm 0.49$ | 1.49<br>$\pm 0.09$  |
| TNBS+Dex30 30 $\mu$ g/kg | 1.00<br>$\pm 0.00$  | 1.14<br>$\pm 0.34$          | 1.14<br>$\pm 0.34$ | 1.14<br>$\pm 0.34$ | 0.71<br>$\pm 0.45$ | 1.00<br>$\pm 0.75$ | 1.00<br>$\pm 0.53$  | 1.00<br>$\pm 0.75$ | 1.00<br>$\pm 0.75$ | 1.01<br>$\pm 0.13$  |
| Dex5 5 $\mu$ g/kg        | 0.00<br>$\pm 0.00$  | 0.14<br>$\pm 0.34$          | 0.00<br>$\pm 0.00$ | 0.14<br>$\pm 0.34$ | 0.00<br>$\pm 0.00$ | 0.00<br>$\pm 0.00$ | 0.28<br>$\pm 0.45$  | 0.00<br>$\pm 0.00$ | 0.00<br>$\pm 0.00$ | 0.06<br>$\pm 0.10$  |
| Dex30 30 $\mu$ g/kg      | 0.00<br>$\pm 0.00$  | 0.00<br>$\pm 0.00$          | 0.00<br>$\pm 0.00$ | 0.00<br>$\pm 0.00$ | 0.14<br>$\pm 0.34$ | 0.00<br>$\pm 0.00$ | 0.28<br>$\pm 0.45$  | 0.00<br>$\pm 0.00$ | 0.00<br>$\pm 0.00$ | 0.04<br>$\pm 0.10$  |

Data were presented as mean  $\pm$  S.D.; \*symbol represents the significance between TNBS and TNBS-Dex5 or TNBS-Dex30 groups (p<0.05)

### Ultrastructural Analysis

By electron microscopy, tubular and glomerular components were observed in normal ultrastructural view in naïve (Figure 3A, 3B), Dex5 (Figure 4A, 4B) and Dex30 (Figure 4C, 4D) groups. TNBS administration induces widespread alterations in ultrastructural view of kidney cells such as; vacuole formation, lysosome accumulation within the tubular cells and thickening of the tubular basement membranes and mitochondrial matrix condensation. Narrowing urinary space and closure filtration slits was evident. Cytoplasmic condensation in podocytes was noticed (Figure 3C, 3D). Dexmedetomidine administration after TNBS induction partially preserved tubular and glomerular structures in both doses (Figure 3E, 3F and Figure 3G, 3H; respectively). Glomerular diameter was significantly reduced in TNBS group (Table 2).

Dexmedetomidine administration during TNBS induction significantly elevated diameter in comparison to TNBS group (p=0.042; p= 0.012 for TNBS+Dex5 and TNBS+Dex30 groups,

respectively). However, that elevation never reached to levels of control group animals.

**Table 2.** Glomerular diameters of each group

| Groups                       | Glomerular diameter ( $\mu$ m) |
|------------------------------|--------------------------------|
| Control                      | 73.97 $\pm$ 3.79               |
| TNBS                         | 56.22 $\pm$ 3.73*              |
| TNBS+DEX5 (5 $\mu$ g/kg)     | 61.75 $\pm$ 5.48               |
| TNBS + DEX30 (30 $\mu$ g/kg) | 70.15 $\pm$ 3.36               |
| DEX5 (5 $\mu$ g/kg)          | 72.80 $\pm$ 2.53               |
| DEX 30(30 $\mu$ g/kg)        | 75.43 $\pm$ 4.43               |

Data were presented as mean  $\pm$  S.D.; \*symbol represents the significance between TNBS and TNBS-Dex5 or TNBS-Dex30 groups (p<0.05)

### Biochemical results

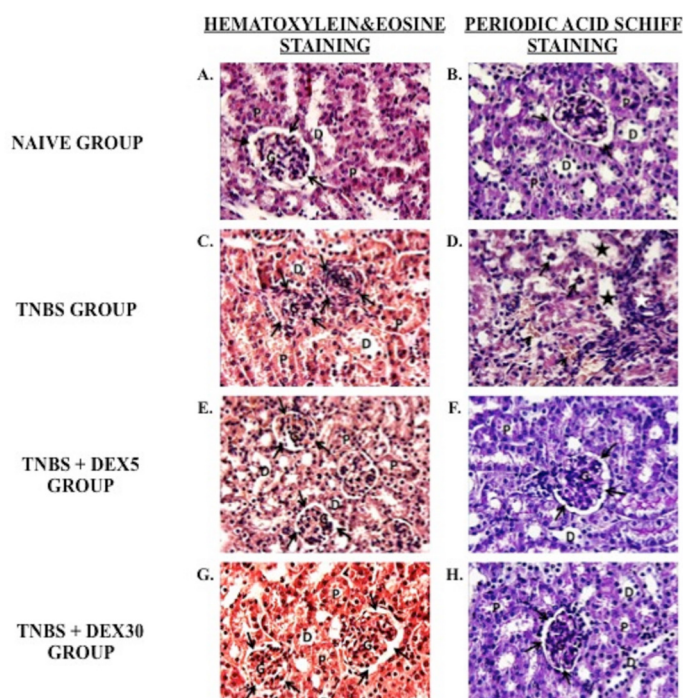
In order to assess functional differences of kidneys in all groups we investigated serum creatinine levels. We observed that TNBS

induction induce a significant elevation on serum creatinine levels in TNBS group in comparison to healthy control group. Administration of dexmedetomidine significantly reduced creatinine levels both at 5µg/kg and 30µg/kg dexmedetomidine concentrations ( $p=0.036$ ;  $p=0.022$ ; respectively).

Tissue MDA, GSH levels and SOD activities are summarized in Table 3. Administration of dexmedetomidine alone did not alter levels of MDA, GSH levels or on SOD at both doses in comparison to control group. Colitis induction by TNBS administration caused 1.46 times elevation on MDA level in comparison to control group. However, administration of dexmedetomidine after TNBS induction significantly reduced MDA level at two different doses. Increasing Dexmedetomidine concentration during TNBS induction did not persuade an additive effect on that reduction.

In case of GSH level, TNBS induction caused significant reduction in comparison to control group. Administration of dexmedetomidine after TNBS induction brought back GSH level to control level. Similar to MDA, increasing dexmedetomidine concentration did not increase GSH level proportionally.

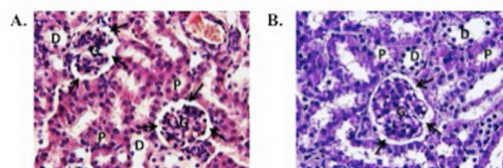
SOD activity reduced 1.55 times after TNBS induction in comparison to control group. Administration of dexmedetomidine at 5µg/kg concentration significantly increased SOD activity 1.48 times in comparison to TNBS group. That elevation reached to 1.96 times at TNBS+Dex30 group in comparison to TNBS group. We did not observe any significant difference in SOD activity between TNBS+Dex5 and TNBS+Dex30 groups.



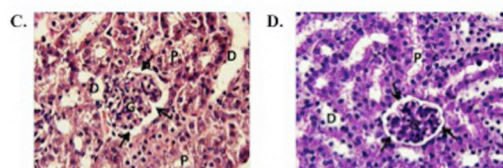
**Figure 1.** Hematoxyline & Eosine (1A, 1C, 1E, 1G) and periodic acid schiff (1B, 1D, 1F, 1H) staining in naive, TNBS, TNBS+Dex5, TNBS+Dex30 groups (x40). D, means distal tube; G, means glomerulus; M, represents mitochondrion; P, proximal tubes. In figures 1A and 1B arrows show Bowman spaces. In figure 1C, 1D arrows Show disappearance of Bowman spaces and vascular congestion; respectively. In figure 1D White aster represents interstitial fibrosis and inflammatory cell infiltration; black asters represent epithelial degeneration in distal tubules. In figure 1E arrows show narrowed Bowman spaces. In figure 1G arrows Show Bowman spaces similar with in naive groups. Scale bar = 2µm.

## HEMATOXYLEIN&EOSINE STAINING PERIODIC ACID SCHIFF STAINING

### DEX5 GROUP

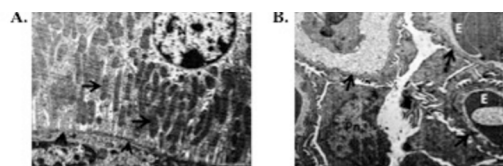


### DEX30 GROUP

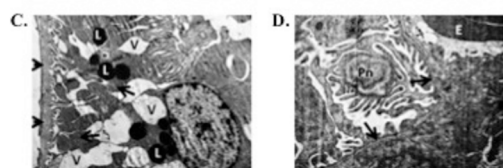


**Figure 2.** Hematoxyline & Eosine (2A, 2C) and periodic acid schiff (2B, 2D) staining in Dex5 and Dex30 groups (x40). Arrows show Bowman spaces similar with naïve groups. Scale bar = 2µm.

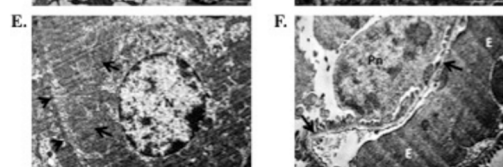
### NAIVE GROUP



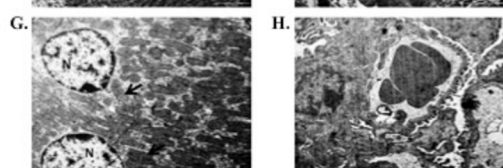
### TNBS GROUP



### TNBS + DEX5 GROUP

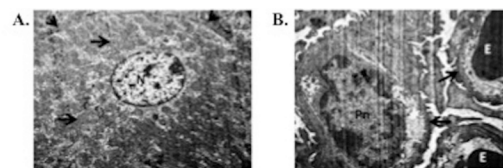


### TNBS + DEX30 GROUP

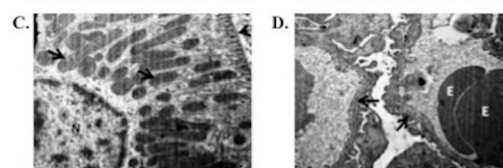


**Figure 3.** Ultrastructural views of naïve, TNBS, TNBS+Dex5 and TNBS+Dex30. In views N, represents proximal tubule epithelial cell nucleus; L, represents lysosomes, V, intracellular vacuoles; Pn, podocyte nucleus; E, erythrocytes in capillary lumen. In figure 3A and 3B arrows show mitochondrion, arrow heads show basal membrane. In views of TNBS group, arrows show mitochondrion and arrow heads show basal membrane. In figure 3E arrows show mitochondrion, arrow heads show basal membrane. In figure 3F arrows show mitochondrion; in figure 3G, arrow shows glomerular basal membrane. Scale bar = 2µm.

### DEX5 GROUP



### DEX30 GROUP



**Figure 4.** Ultrastructural views of Dex5 (4A, 4B) and Dex30 (4C, 4D) groups. In figure 4A, arrows represent mitochondrion and arrow heads show basal membrane. In figure 4B, arrows show glomerular basal membrane. In figure 4C, arrows show mitochondrion and arrow head shows basal membrane; in figure 4D, arrows show glomerular basal membrane. Scale bar = 2µm

Table 3. Serum creatinine, MDA; GSH and SOD levels in tissue homogenates of each group

| Groups                  | Serum creatinine (mg/dL.) | MDA (nmole/mg)            | GSH (nmole/mg)          | SOD (U/mg)              |
|-------------------------|---------------------------|---------------------------|-------------------------|-------------------------|
| Control                 | 0.23 ± 0.02               | 740.0 ± 64.2              | 1293.3±74.3             | 138.0±43.4              |
| TNBS                    | 0.38 ± 0.03*              | 1084.3±205.8 <sup>+</sup> | 901.6±95.7 <sup>#</sup> | 88.8±13.5 <sup>\$</sup> |
| TNBS + DEX5 (5 µg/kg)   | 0.31 ± 0.01               | 870.2± 75.65              | 1283.4±93.3             | 131.9±57.6              |
| TNBS + DEX30 (30 µg/kg) | 0.28 ± 0.02               | 837.5± 180.5              | 1358.2±293.2            | 174.5±28.8              |
| DEX5 (5 µg/kg)          | 0.25 ± 0.02               | 800.55±34.6               | 1290±74.8               | 128.2±31.9              |
| DEX30 (30 µg/kg)        | 0.24 ± 0.03               | 790.0±64.2                | 1207.1±71.3             | 138.0±43.4              |

Data were presented as mean ± S.D.; \*, <sup>+</sup>, <sup>#</sup>, <sup>\$</sup> symbols represent the significancy between TNBS and TNBS-Dex5 or TNBS-Dex30 groups in serum creatinine, MDA, GSH, SOD; respectively (p<0.05)

## Discussion

Inflammatory bowel disease (IBD) induced renal failure is a discomfort that should not be ignored during preoperative and postoperative periods. Inflammatory bowel disease together with analgesic induced nephropathy can cause severe consequences on kidney. In this study we aimed to investigate the effect of dexmedetomidine, a sedative and analgesic agent used in intensive care units and perioperative period, on renal tissue histology and renal oxidative stress during IBD. It is known that IBD cause renal impairment and thus, reduction on renal function. However, there is a big dilemma whether that impairment is associated with the treatment applications of IBD. Today, there is still a conflict about that issue. There are some reports informing that 5-aminosalicylate (5-ASA) or mesalazine (5-ASA + resins or gels) do not induce nephrotoxicity during IBD treatment. They put forward the idea that IBD itself induce renal impairment. Indeed; chronic IBD is seldom complicated by renal function disorder; and when that occurs the consequences are usually serious either can be caused by treatment options or the analgesics that are used during the medical applications.

Critically ill patients exhibit a high risk of acute kidney injury. Acute kidney injury is still associated with higher rates of infection and gastrointestinal bleeding. Even patients with only minor changes on serum creatinine levels are exposed high mortality rate. Furthermore, long term regular ingestion of one or more analgesic medications may cause renal insufficiency [15,16]. Therefore, using analgesics that do not induce inflammatory process during treatment and diagnosis is an important issue.

In our study firstly, we emphasize that experimental IBD model induce serious renal damage and impairs renal function. In concern of reducing renal damage in our study we treated IBD induced mice by parenteral dexmedetomidine administration. Current studies, proved that dexmedetomidine has cytoprotective effect during renal ischemia and it establishes that effect by improving hypoxemia induced apoptosis in proximal tubular cells [17,18]. Besides, Si et al. proved that renoprotective function of Dexmedetomidine depends on anti-apoptotic effect via inhibiting JAK2/STAT3 signaling pathway [19]. In our study we demonstrated that protective effect by electron microscopic investigation and renoprotective effect of dexmedetomidine was observed clearly in ultrastructural views of kidney tissues.

The occurrence of impaired oxidative status is marked by several

biomarkers, among them, malondialdehyde (MDA) which is a terminal compound of lipid peroxidation, is mostly used as an index of oxidative stress. Fonseca et al. proved that malondialdehyde is an early predictive marker of renal dysfunction in transplant patients [20]. Therefore, investigating MDA levels in kidney tissues would be beneficial to understand the illness of kidney after dexmedetomidine administration. We showed that MDA level increased in kidney tissue during experimental colitis model and dexmedetomidine administration reduced MDA level.

Protective effect of dexmedetomidine on ischemic reperfusion injury has been reported in several number of research articles for distinct organs [21-23]. In case of renal protection dexmedetomidine reduces renal vascular resistance and increases the glomerular filtration rate [24]. In support of these findings, we observed preserved tubular and glomerular structures in Dexmedetomidine administered TNBS groups in histological and ultrastructural examinations. Frumento et al. reported that serum creatinine level was significantly decreased in patients that administered dexmedetomidine after thoracic surgery and that reduction continued for up to a week following surgery [25]. In our study we also observed significant reduction on serum creatinine levels at two different doses of dexmedetomidine in experimental colitis group. Dexmedetomidine ameliorates sepsis induced acute kidney injury by decreasing inflammatory cytokine expression [26]. Similar observation has been reported in case of dexmedetomidine administration in TNBS induced colitis model in which, dexmedetomidine administration switched Th1 inflammatory cytokine toward to Th2 cytokine pathway [12].

## Conclusion

In conclusion, we suggest that the administration of Dexmedetomidine ameliorates the histological and ultrastructural view of renal damage and increases the defense capacity of kidney against oxidative damage during an experimental inflammatory bowel disease.

## Competing interests

The authors declare that they have no competing interest.

## Financial Disclosure

There are no financial supports

## Ethical approval

The experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals adopted by Animal Breeding and Care Center of Inonu University (Ethic No: 2016/A-42).

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