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Dexmedetomidine effect to lung injury in abdominal hypertension

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ABSTRACT

Objective: An experimental study was performed to evaluate the effect of dexmedetomidine on lung injury secondary to experimental intra-abdominal hypertension (IAH).

Methods: Eighteen Wistar-albino rats were included and allocated into 3 groups - the control group (CG, n=6), the sham group (SG, n=6) and the dexmedetomidine group (DG, n=6). No intervention was made in CG. IAH was achieved by insufflating atmospheric air with a percutaneous intraperitoneal needle up to 15 mmHg pressures in SG and DG. At the 60th min of IAH, physiological serum (1.5 ml/100 grams/hr) in SG and dexmedetomidine (1 mcg/kg/hr) in DG were infused for 30 min through the tail vein. At the 90th min, the left inferior lobes of the lung were harvested for biochemical (nitric oxide-NO, malondialdehyde-MDA) and histopathological (alveolar hemorrhage, edema, congestion, leukocyte infiltration) examination.

Results: There was no significant difference between any of the groups with regards to NO and MDA levels ($p>0.05$). Histopathologically, although alveolar hemorrhage, edema, congestion, leukocyte infiltration were increased in SG compared to CG and DG, the difference was not statistically significant ($p>0.05$). There was no significant difference between CG and DG with respect to histopathological grading ($p>0.05$).

Conclusion: IAP of 15 mmHg in rats causes mild injury in lung parenchyma. The administration of DEX in clinical doses does not seem to significantly affect the lungs of rats.

Key words: *Intra-abdominal hypertension, lung injury, dexmedetomidine*

Introduction

The intra-abdominal pressure (IAP) exceeding 12 mmHg is called intra-abdominal hypertension (IAH) which has deleterious pathophysiological consequences [1,2]. IAH can be encountered in many clinical conditions, such as trauma, retro-/intra- abdominal bleeding, pancreatitis, aggressive fluid resuscitation, intestinal obstruction, tumors and pneumoperitoneum for laparoscopy [1,2]. As it has respiratory, renal, splanchnic, and cerebral complications, much effort has gone in to diagnosis and managing IAH in the last decade. Besides well-known management principles consisting of serial monitoring of IAP, optimization of systemic perfusion and urgent surgical decompression,

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sedation and analgesia have also been recommended so as not to worsen the scenario by agitation and ventilator dyssynchrony [1].

Dexmedetomidine is a specific α2-adrenoreceptor agonist which is commonly used for sedation [3]. It has neuroprotective, cardioprotective and renoprotective properties besides its well-known sedative, analgesic and anxiolytic functions [3]. In recent studies, it has been shown that dexmedetomidine also possesses anti-inflammatory effects [3-5]. It has been reported that dexmedetomidine has a dose dependent beneficial effect on lung injury secondary to sepsis [4], pulmonary contusion [5], and ventilator-induced lung injury [6]. However, there is little known about dexmedetomidine effects on lung injury secondary to increased intra-abdominal pressure. Therefore, an experimental study was conducted to evaluate the effect of dexmedetomidine on lung injury secondary to intra-abdominal hypertension (IAH).

Materials and Methods

The experiments were performed after ethical approval by Ankara Local Ethical Committee (Approval No: 04.06.2013/0014-212) and under the recommendations of the Principles of Laboratory Animals Care.

Animals

Eighteen Wistar albino rats, weighing 200-250 g, were used for the experiments. The rats were kept at 22^{0}C room temperature and a 12 hour day/night cycle. Standard laboratory rodent chow and tap water were available freely. The rats were allocated in to 3 groups - the control group (CG, n=6), the sham group (SG, n=6) and the dexmedetomidine group (DG, n=6). In CG, no intervention was made. In SG, IAH was performed and 1.5 ml/100 grams/hr physiological serum was infused. In DG, IAH was performed and dexmedetomidine at a clinical dose of 1 mcg/kg/hr (Precedex, 100 μg/ml; Abbott, Istanbul, Turkey) was infused [6].

Experimental protocol

The rats were anesthetized with ketamine hydrochloride (40mg/kg, Ketalar^R, Pfizer Warner Lambert, Istanbul, Turkey) and Xylazine hyrochloride (5mg/kg, Alfazyne, Alfasan Int BV, Woerden, Holland). The animals were placed in the supine position during the experiments. They were spontaneously breathing 100% oxygen. A 20 G 32 mm needle was inserted percutaneously into the peritoneal cavity. Atmospheric air was insufflated into the abdominal cavity with the help of a manual insufflator with manometer (aneroid sphygmomanometer, Mentone, Victoria, Australia). As a consequence of the rats spontaneously breathing, IAP was kept at 15 mmHg during the experiments in SG and DG as described in the literature [7].

The tail veins of the animals in SG and DG were catheterized with a 24 G angiocath. At the 60th min of IAH, physiological serum (1.5 ml/100 grams/hr) in SG and dexmedetomidine (1 mcg/kg/hr) in DG were infused for 30 min through the tail vein.

At the 90th min, left inferior lobes of the lungs were harvested by median sternotomy and the animals were sacrificed by exsanguinations. The harvested lung tissues were analyzed biochemically for nitric oxide-NO, malondialdehyde-MDA levels determination, and histopathologically for alveolar hemorrhage, edema, congestion and leukocyte infiltration examination.

Histopathological examination

The lung tissues were fixed in 10% formalin and dehydrated with ethanol solution and cleared with xylene. Then, all samples were embedded in paraffin. Tissues were sectioned in 5 μm pieces and stained with routine a hematoxylin and eosin stain. One blinded pathologist examined the specimens under a light microscope (Olympus CX31, Dublin, Ireland). The lungs were graded for each histopathological finding (alveolar edema, congestion, hemorrhage, leukocyte infiltration) separately, and the points were added up to get a total pathology score (Table 1).

Biochemical examination

All lung tissues were kept at -80°C, and then washed with 0.9% NaCl. The tissues were homogenized (Labor Technique, Müllheim, Germany) with 0.9% NaCl solution 1 mL in ice, and centrifuged at 1,500 g for 10 minutes at 4°C. The supernatants were used for malonyl dialdehyde (MDA) and total nitrite/nitrate (NO) protein determinations. Protein levels were measured by the method of Lowry et al. [8].

NO levels were measured through a spectrophotometric method with the techniques described by Miranda et al. [9]. Nitrate was reduced to nitrite with vanadium (III) and then nitrite levels were measured by using Griess reagents. The results were expressed in

Table 1. The histopathological grading system of the lungs in the present work.

	Intra-alveolar hemorrhage	Alveolar edema	Congestion	Leukocyte infiltration
Grade 0	Absent	Absent	Absent	Absent
Grade 1	Mild (<10%)	Mild (<10%)	Mild (<10%)	Mild (< 10 leukocyte/40 HPF)
Grade 2	Moderate (15-20%)	Moderate (15-20%)	Moderate (15-20%)	Moderate (10-45 leukocyte/40 HPF)
Grade 3	Severe (20-25%)	Severe (20-25%)	Severe (20-25%)	Severe (>45 leukocyte/40 HPF)

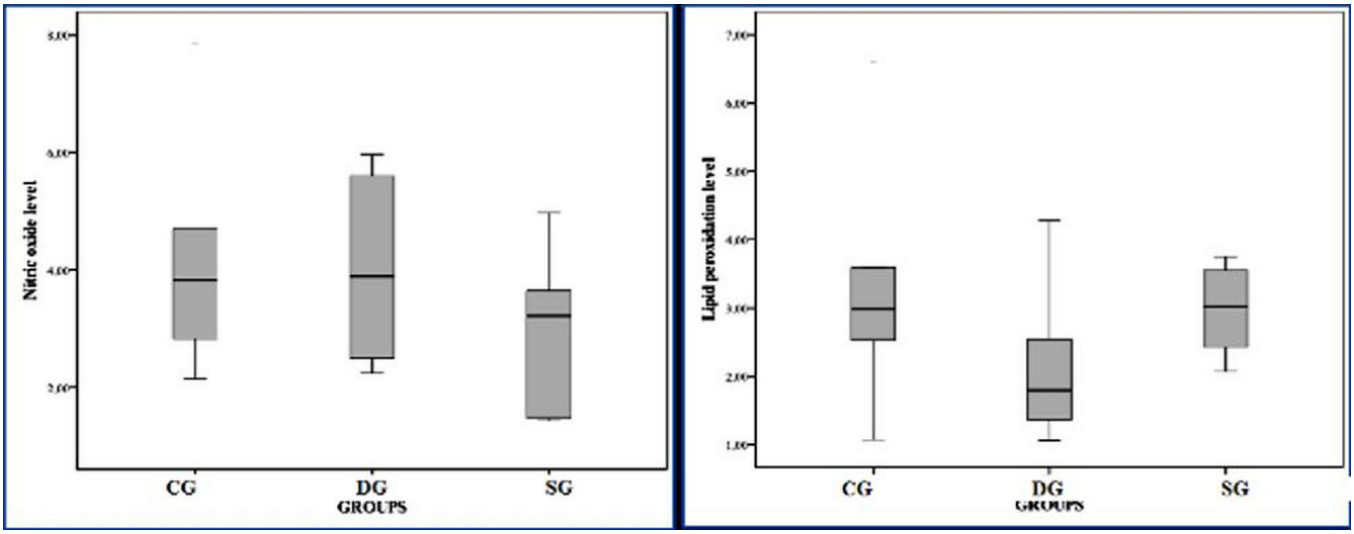

Figure 1. The comparison of nitric oxide (NO) and lipid peroxidation (MDA) levels. (**CG:** control group, **SG:** sham group, **DG:** dexmedetomidine group)

μM/mg protein.

MDA levels were measured by the modified method of Yagi, documented earlier by Armstrong and Al-Awadi [10]. The calibration curve was prepared with 1, 1, 3, 3-tetraethoxypropane (Sigma, St Louis, MO) standards of 1- to 25-nmol/L dilutions. The results were expressed in nM/mg protein.

Statistics

The results (NO and MDA levels) arranged ordinarily were analyzed with a one-way analysis of variance (ANOVA) test. Other data arranged non-ordinarily were analyzed with a Kruskal-Wallis test. The post-hoc comparisons were performed by a Mann Whitney U test (SPSS 15.0, SPSS Inc., Chicago, USA). p values lower than 0.05 were considered significant.

Results

All animals survived during the experiments but they had short-lasting irregular breathing after dexmedetomidine infusion.

Biochemically, NO levels were slightly decreased and MDA levels were slightly increased in SG compared to CG. However, there was no significant difference between groups regarding to NO and MDA levels ($p>0.05$) (Figure 1).

Histopathologically, there was mild alveolar hemorrhage and edema with slightly increased leukocyte infiltration in CG, probably resultant of surgical manipulation. In SG, there was moderate to severe alveolar hemorrhage and edema with increased leukocyte infiltration. In the lung tissues of DG, there was mild to moderate alveolar hemorrhage and edema with increased leukocyte infiltration. The microscopic appearances of the lungs from each group are provided in Figure 2. Although histopathological grades were increased in SG compared to CG and DG, the difference was not statistically significant ($p>0.05$). There was no significant difference between CG and DG regarding histopathological grading ($p>0.05$).

Discussion

Elevated intra-abdominal pressure (IAP) is a threat not only to local tissues, but also to adjacent organs like the lungs. Increased IAP causes elevation of the

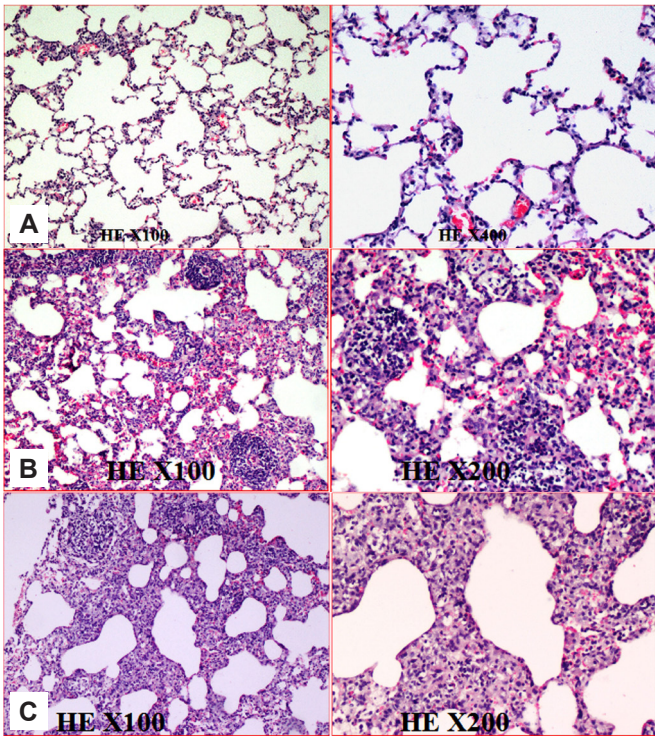

Figure 2. The histopathological examination of the samples (H&E, X100, X200, X400). **(A)** Control group; mild alveolar hemorrhage, edema and slightly increased leukocyte infiltration. **(B)** Sham group; moderate to severe alveolar hemorrhage, edema and increased leukocyte infiltration. **(C)** Dexmedetomidine group; mild to moderate alveolar hemorrhage, edema and increased leukocyte infiltration.

diaphragm upwards compressing the lungs in the thoracic cavity [1,2]. The compression of the lungs lead to atelectasis - mostly in the lower lobes – and reduced pulmonary blood flow, followed eventually by infection and inflammation [2]. As a consequence, respiratory failure develops and mortality is usually inevitable. These effects appear to begin with 15 mmHg and increase when the pressure is further elevated [2,11]. Therefore, early recognition of IAH and management of hemodynamics is critical. As a result of pain, ventilator dyssynchrony and agitation will increase IAP further, so these patients are mostly sedated [1,2].

In the present study, IAP was increased up to 15 mmHg, enough to create IAH but not abdominal compartment syndrome as the animals were spontaneously breathing. The biochemical results of the present work showed that this model did not induce oxidative injury in the lungs. In previous studies, the metabolic alterations caused by the absorbed CO2 gas were blamed for the oxidative damage seen in pneumoperitoneum rather than the effect of increased IAP [7,12]. One can speculate that oxidative damage in lungs was not detected because atmospheric air to increase IAP was utilized. In contrast, histopathological examination revealed that the authors' model of IAH caused histopathologic alterations in lung tissues of the rats, although statistical significance was not present. The reason for this non-significant mild alteration may be related to the pressure levels maintained during the experiments. On the other hand, these results confirm the literature data revealing that IAP at moderate to low levels minimizes organ injury and other complications of IAH [7].

Dexmedetomidine is a highly specific α2-adrenoreceptor agonist. It is commonly used for post-operative sedation [3]. Its neuroprotective, cardioprotective and renoprotective properties make it useful in sedation of many clinical conditions, such as epilepsy, awaken procedures, cardiac surgery and bariatric surgery [3]. In addition, it causes less respiratory depression [3]. Dexmedetomidine can also be used in sedation of the patients with IAH because of these advantages.

Dexmedetomidine has been shown to have anti-inflammatory effects in various animal studies. It was reported that it has a beneficial effect on lung injury secondary to sepsis [4], pulmonary contusion [5] and ventilator-induced lung injury [6]. However, this anti-inflammatory effect cannot be seen in clinically relevant doses [6,13]. Yang et al. (2008) reported that the anti-inflammatory effect of dexmedetomidine can be achieved when it is used at a dosage 10 times higher than clinically relevant doses [6]. However, the use of dexmedetomidine at such higher doses causes bradicardia and hypotension [14]. Geze et al. (2012) also used dexmedetomidine at high doses to prevent pulmonary injury after pneumoperitoneum [15]. They concluded that dexmedetomidine at high doses has a protective effect on the lungs after CO2 pneumoperitoneum in ventilated rats [15].

In the present study, dexmedetomidine was used at clinically relevant doses since the animals were spontaneously breathing. The animals did not experience any adverse effects except short-lasting breathing irregularities. The decrease of the histopathological grades in the dexmedetomidine group compared to the sham group show that it has a slightly beneficial effect on lung injury in IAH, although there was no statistical significance. The reason for this might be the dosage of dex-

medetomidine employed or the small numbers of animals used in the experiment. Therefore, future studies with a greater number of animals at different doses of dexmedetomidine and under different ranges of IAPs may yield more comprehensive results.

Overall, the present experimental model of IAH caused mild injury in the lungs. Although not statistically significant, administration of dexmedetomidine in clinical doses seems to reverse mild injury in the lungs secondary to IAH.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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