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Can Angiotensin Converting Enzyme Inhibitors Prevent Postoperative Adhesions?

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Background. **Peritoneal adhesions are pathological fibrotic bands developing after mesothelial damage. Transforming growth factor beta-1 (TGF-β1) has mitogenic activities for macrophages and fibroblasts. Overexpression of TGF-β1 has been implicated in the pathogenesis of several fibrotic disorders. Angiotensin II increases the expression of the TGF-β1 in fibroblasts. The aim of the study was to investigate the effect of angiotensin converting enzyme inhibitor (ACE) on intraperitoneal adhesions.**

Materials and methods. **Thirty male Wistar albino rats were divided into two groups. In the first procedure, laparotomy was performed through a 3-cm midline incision. Ileum was divided above 10 cm from ileocecal valve and a single-layer ileoileal anastomosis was performed. Although no treatment was given to rats in group 1, lisinopril (an ACE inhibitor) was given to rats in group 2 for postoperative 7 days in drinking water. Estimated amount of supplied lisinopril was 6.5 mg/kg/day. On postoperative 8th day, relaparotomy was performed and adhesions were evaluated. At the same time, blood samples were taken for TGF-β1 measurements.**

Results. **Adhesion severity was significantly less in the ACE inhibitor group ($P < 0.001$). While mean TGF-β1 level was 860.3 ± 108.1 pg/dl (mean ± SD) in control group, it was 335.8 ± 52.4 pg/dl in ACE inhibitor group ($P < 0.001$). There was a significant correlation between serum TGF-β1 levels and grade of adhesions ($r = 0.948$).**

Conclusion. **It was concluded that ACE inhibitors might be useful for preventing peritoneal adhesions.**

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INTRODUCTION

Peritoneal adhesions are defined as pathological fibrotic bands developed between any surfaces in the peritoneal cavity. For the development of adhesions between two surfaces inside the peritoneum, there must be peritoneal mesothelial damage on at least one surface [1]. Despite recent advances in adhesion prevention, the pathogenesis of adhesion formation is still not well understood [2]. A few hours after the mesothelial damage, fibrinous exudate is released. When the exudate is absorbed, fibrous bands and newly formed capillary vessels remain at the site and structures form the permanent fibrotic adhesions [1, 3].

Transforming growth factor beta-1 (TGF-β1), a polypeptide cytokine with potent chemoattractant and mitogenic activities for macrophages and fibroblasts, is capable of stimulating the expression of various extracellular matrix components by fibroblasts. The overexpression of TGF-β1 has been implicated in the pathogenesis of several fibrotic disorders at various sites throughout the body such as pulmoner fibrosis, glomerulonephritis, cirrhosiss of liver, and skin scarring, as well as peritoneal adhesion formation [4–8]. A variety of physiological roles of angiotensin II (AT-II) have been clarified not only in the pathogenesis and maintenance of high-blood pressure [9] but also in the stimulation of fibroblast proliferation and collagen synthesis by non-paranchymal cells [10–12]. AT-II increases the expression of the TGF-β1 and collagen I genes in lung fibroblasts and stimulates the proliferation of mesengial cell [10, 13]. It was shown that an

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TABLE 1

Adhesion Grading According to Evans Model

Grade	Grading of adhesions
0	No adhesions
1	Spontaneously separating adhesions
2	Adhesions separating by traction
3	Adhesions separating by dissection

angiotensin-converting enzyme (ACE) inhibitor suppressed progression of hepatic fibrosis in rats [14].

Because TGF-β1 and AT-II appear to play a pivotal role in various fibrotic disorders including peritoneal adhesion formation, we hypothesized that ACE inhibitors can be reduce intraperitoneal adhesions by decreasing AT-II and consequently TGF-β1 levels. In this study, we aimed to investigate effects of ACE inhibitors on intraperitoneal adhesions in rats with ileoileal anastomosis.

MATERIALS AND METHODS

This study was conducted in Firat University, Faculty of Medicine, Experimental Animal Raising and Research Laboratory after approval of The Local Ethics Committee. Thirty male Wistar rats weighing 200 to 224 g were used. The animals were acclimatized for 1 week before the experiments. The animals were kept in individual cages. They were housed in constant temperature rooms and given standart rat chow. Only water was provided in the 12 h preceding the experiments.

The rats were divided randomly into two groups, a control group (group 1, $n = 15$) and ACE inhibitor group (group 2, $n = 15$). They were anesthetized with a combination of intramuscular 5 mg/kg xylasine (Bayer, İstanbul, Turkey) and 30 mg/kg ketamine hydrochloride (Parke-Davis, İstanbul, Turkey) and breathed spontaneously throughout the procedures. The mid-abdominal area was shaved and prepared with povidone iodine. The peritoneal cavity was entered through a 3-cm midline incision. Ileum was divided above 10 cm from ileocecal valve and a single-layer ileoileal anastomosis was performed with 6.0 polypropylen (Prolene; Ethicon, Hamburg, Germany) continuous sutures. The abdominal incision was closed with 3.0 silk sutures. All animals were given water only on the first post-operative day; standart rat chow and water were provided on the second post-operative day.

Although no treatment was given to rats in group 1, Lisinopril (Zestril tb, Abdi Ibrahim, Istanbul, Turkey) was given as the ACE inhibitor to rats in group 2. Lisinopril was dissolved in the animals' drinking water at 50 mg/l concentration and was given *ad libitum* via free drinking by starting 12 h before from ileoileal anastomosis throughout postoperative 7 days. A rat would drink water at a rate of 130 $\pm$ 6 ml/kg per day (or about 25 ml/day). So, estimated amount of supplied lisinopril was 6.5 mg/kg per day [15]. The volume of residual water was recorded every day and daily lisinopril consumption was straightened.

On postoperative 8th day, rats were anesthetized as described above and re-laparotomy was performed with a reversed U-shaped incision of the anterior abdominal wall, which was retracted, caudally to provide maximal exposure. Adhesions were graded as described by Evans *et al.* [16] (Table 1). Then blood samples were taken from inferior vena cava for TGF-β1 measurements and rats were sacrificed with overdoses of ketamine and xylasine mixture. These samples were stored at -80°C until analysis. TGF-β1 content of serum was determined by using enzyme-linked immunosorbent assay kits specific for TGF-β1 (Biosource Immunoassay Kit, Camarillo, CA).

A Mann-Whitney *U*-statistic as a non-parametric test was used to determine difference in adhesion grading and the unpaired Student's *t* test was used to analyze TGF-β1 data. A P value < 0.05 was considered significant. A simple linear regression analysis was used to determine the correlation between serum TGF-β1 levels and adhesion grades.

TABLE 2

Adhesion Grading of the Groups ($P < 0.001$ According to Mann-Whitney U-test)

Grade	Control group	ACE inhibitor group
0	—	6 (40%)
1	—	9 (60%)
2	5 (33%)	—
3	10 (66%)	—

RESULTS

The grading of adhesions in groups is summarized in Table 2. In the control group, there were five rats (33%) in grade 2 and 10 rats (66%) in grade 3. In the ACE inhibitor group, there were nine rats (60%) in grade 1 and six rats (40%) grade 0. Comparison of two groups indicated that adhesion severity was highly significantly less in the ACE inhibitor group ($P < 0.001$). Although mean TGF-β1 level was 860.3 $\pm$ 108.1 pg/dl (mean $\pm$ SD) in control group, it was 335.8 $\pm$ 52.4 pg/dl in ACE inhibitor group ($P < 0.001$) (Fig. 1). Serum TGF-β1 levels were well correlated with grade of adhesions ($r = 0.948$, $P < 0.001$) (Fig. 2).

DISCUSSION

Peritoneal adhesions do not only lead to small bowel obstruction, but they also lead to difficult re-operations

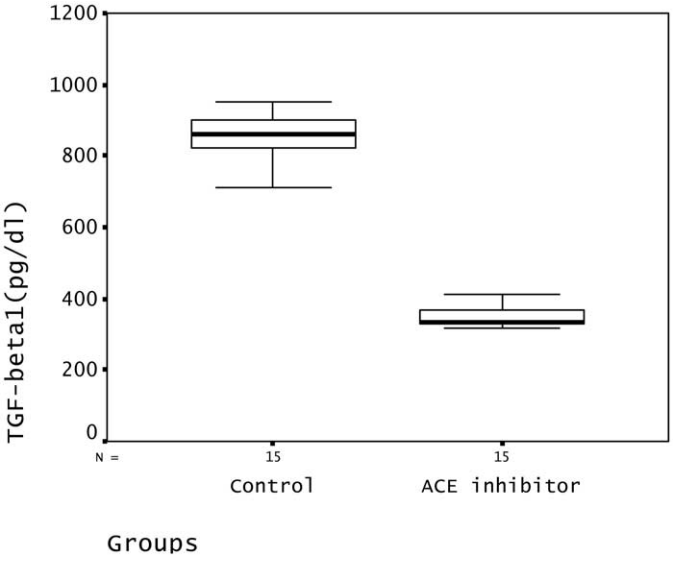

FIG. 1. Serum TGF-β1 levels in groups ($P < 0.001$).