

# The effect of carbon dioxide pneumoperitoneum on the severity of peritonitis

## Karbondioksit pnömoperitonyumun peritonitin şiddeti üzerine etkisi

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### BACKGROUND

There are still some doubts regarding the reliability of laparoscopic interventions in the presence of generalized peritonitis. The aim of the present experimental study was to investigate the effects of carbon dioxide (CO<sub>2</sub>) pneumoperitoneum on inflammatory response and peritonitis severity score in experimental peritonitis.

### METHODS

21 Wistar albino rats were used in the study. The rats were distributed into three groups: the control group (Group 1, n=7), the bacterial peritonitis-induced group (Group 2, n=7), and the peritonitis+CO<sub>2</sub> pneumoperitoneum-induced group (Group 3, n=7). In Groups 2 and 3, peritonitis was induced by intraperitoneally injected *Escherichia coli*. In Group 3, pneumoperitoneum was induced by giving CO<sub>2</sub> insufflations. The rats were sacrificed 24 hours later. Five cc of blood was sampled, and peritoneum tissue was excised from the abdominal region of the rats. Peritonitis severity score, C-reactive protein level and white blood cell count were assessed in all groups.

### RESULTS

Peritonitis severity score, C-reactive protein level and white blood cell count were significantly higher in Groups 2 and 3 than Group 1 (both, p<0.05), while significantly lower in Group 3 than Group 2 (p<0.05).

### CONCLUSION

The results of this study show that CO<sub>2</sub> pneumoperitoneum decreases peritonitis severity and systemic inflammatory response in experiments with *E. coli*-peritonitis and sepsis.

**Key Words:** Carbon dioxide; intraabdominal sepsis; laparoscopy; peritonitis; pneumoperitoneum; rat.

### AMAÇ

Jeneralize peritonit olgularında hala, laparoskopik girişimlerin güvenilirliği ile ilgili kaygılar devam etmektedir. Bu deneysel çalışmada, deneysel peritonit oluşturulan sıçanlarda karbondioksit (CO<sub>2</sub>) pnömoperitonyumun enflematuvar cevap ve peritonit şiddeti üzerine etkilerinin araştırılması amaçlandı.

### GEREÇ VE YÖNTEM

Çalışmada 21 Wistar albino cinsi sıçan kullanıldı. Sıçanlar üç gruba ayrıldı. Bunlar; kontrol (grup 1), bakteriyel peritonit oluşturulan grup (grup 2) ve peritonit + CO<sub>2</sub> pnömoperituan oluşturulan grup (grup 3) idi. İkinci ve üçüncü gruptaki sıçanların periton içine *Escherichia coli* verilerek peritonit oluşturuldu. Üçüncü gruptaki sıçanlarda CO<sub>2</sub> insüflasyonu ile pnömoperitonyum oluşturuldu. Sıçanlar 24 saat sonra öldürüldü, kan ve karın duvarından periton örneği alındı. Tüm gruplarda peritonit şiddet skoru, C-reaktif protein düzeyi ve kanda beyaz küre sayısı değerlendirildi.

### BULGULAR

Peritonit şiddet skoru, C-reaktif protein düzeyi ve kan beyaz küre sayısı, ikinci ve üçüncü gruplarda, birinci gruba göre anlamlı düzeyde yüksek bulundu (p<0,05). Üçüncü grupta değerler, ikinci gruptan anlamlı düzeyde düşük bulundu (p<0,05).

### SONUÇ

Çalışmamızın sonuçları, CO<sub>2</sub> pnömoperitonyumun *Escherichia coli* ile peritonit ve sepsis oluşturulan sıçanlarda peritonit şiddetini ve sistemik enflematuvar yanıtı azalttığını göstermiştir.

**Anahtar Sözcükler:** Karbondioksit; karınıçi sepsis; laparoskopi; peritonit; pnömoperitonyum; sıçan.

In abdominal surgery, laparoscopic interventions, due to their numerous advantages, are preferable to open surgery. However, the presence of peritonitis was considered as a contraindication for laparoscopic surgery.<sup>[1]</sup> Even today, there is controversial discussion on the effect of pneumoperitoneum in the presence of generalized peritonitis. There are many opposing views about the effect of pneumoperitoneum on peritonitis.<sup>[2]</sup> It has been reported by some experimental studies that carbon dioxide (CO<sub>2</sub>) pneumoperitoneum has a protective effect against bacterial peritonitis induced in rats and reduces the risk of bacteremia in endotoxemia.<sup>[3-10]</sup> Using CO<sub>2</sub> as an antimicrobial agent in the food industry may be considered as evidence for this opinion.<sup>[11]</sup> In contrast, others think that pneumoperitoneum has a potential worsening effect on underlying intraabdominal sepsis. It has been suggested that increasing gas pressure associated with the gases used for pneumoperitoneum and turbulence due to continuous gas infusion facilitate the dissemination of pathogen microorganisms and increase the severity of peritonitis.<sup>[12-14]</sup> Some studies have shown that increased intraabdominal pressure via pneumoperitoneum may lead to the increased risk of bacterial translocation and bacteremia.<sup>[15-26]</sup> Some studies have shown that CO<sub>2</sub> has immunosuppressive effects on neutrophil and macrophage function, and CO<sub>2</sub>-induced immunosuppression might be deleterious in the setting of infection.<sup>[27,28]</sup> It has been argued as well that CO<sub>2</sub> pneumoperitoneum may cause malignant hypercapnia and toxic shock syndrome in the cases with peritonitis.<sup>[28,29]</sup> At the same time, other studies have shown that pneumoperitoneum has no impact on the systemic dissemination of peritonitis and that laparoscopic surgery preserves peritoneal defence mechanisms.<sup>[3,30-34]</sup>

Our study was designed to research the effect of CO<sub>2</sub> pneumoperitoneum on the severity of peritonitis and inflammatory response in the rats with peritonitis induced by the administration of *Escherichia coli* (*E. coli*) via the intraperitoneal route.

## MATERIALS AND METHODS

The study began after obtaining approval from the Ethical Committee of the Faculty of Medicine (30.06.2004-0.01.00.00.101, 5/47). Twenty-one rats of Wistar albino genus (250-300 g) were used in the study. The whole study was carried out under aseptic conditions. The animals were randomly divided into three groups: the control group (Group 1), the bacterial peritonitis-induced group (Group 2) and peritonitis+CO<sub>2</sub> pneumoperitoneum-induced group (Group 3).

The control group remained untreated. Blood (5 cc) was sampled through the intracardiac route from these rats after the study, after their sacrifice with a

high ether dose. In Group 2, following the antiseptics of the administration site with povidone-iodine solution of 10%, 1 cc of *E. coli* bacilli (ATCC 25922), strain H110 (10<sup>5</sup>/ml), was given intraperitoneally. These rats were sacrificed with a high ether dose 24 hours (h) after the application, and 5 cc of blood was sampled. Similarly, Group 3 was administered 1 cc of *E. coli* (10<sup>5</sup>/ml) through the intraperitoneal route, after the asepsis of the application site. After 24 h, the rats were anesthetized with ether, and pneumoperitoneum was induced by giving CO<sub>2</sub> through the mechanism described below, keeping them under 4 cm of water pressure for 1 h. Blood (5 cc) was sampled from these rats as applied in other groups. After the operation, peritoneum tissue of 1 cm<sup>2</sup> was excised from the abdominal region of the rats of each group.

### Pneumoperitoneum Induction Mechanism

For the transfer of CO<sub>2</sub> gas, a plastic hose was connected to the output of the CO<sub>2</sub> tube. A triple tap was installed to the other end of this hose. A manometer (Cuff Pressure Gauge) was installed to one of the other two ends of this triple tap. A cannula (no. G18) was connected to the remaining end of the tap. CO<sub>2</sub> was given to the rats via the intraperitoneal route by means of this mechanism, through a cannula percutaneously installed into the peritoneum of the rats. The intraabdominal pressure of the rats was measured with a manometer adapted to the system, keeping the water level at 4 cm.

### Biochemical Analysis

Total leukocyte count and C-reactive protein (CRP) values were investigated in the sample blood specimens. The leukocyte count was evaluated by the Cell-Dyne 3700 device (Abbott) and CRP Cobas Integra 800 (Roche) analyzer device.

### Histopathological Evaluations

Peritoneum biopsy specimens were fixed with 10% formalin and then sections were prepared. Preparations were stained with a hematoxylin-eosin stain. Scoring of the severity of histopathological peritonitis was evaluated by observers who were blinded to the groups, and the findings were evaluated as peritonitis scores of 0, 1, 2 and 3, depending on the findings shown in Table 1.<sup>[10,14]</sup>

### Statistical Evaluation

The Statistical Package for the Social Sciences for Windows (version 11.5) (SPSS, Inc., Chicago, IL) was used for the statistical evaluation of the data. For the statistical analyses, nonparametric independent group comparisons were made. For comparisons between groups, the Mann-Whitney test was used if any statistical significance was found. A level of 5% (p<0.05) was established as significant. The data was expressed as mean±SD.

**Table 1.** Scoring criteria of histopathologic findings

Peritonitis score	Scoring criteria of histopathologic findings
0	No sign of inflammation or tissue alteration
1	Dilatation of subserosal capillaries, dulling of the peritoneal surface, and swelling of mesothelial cells
2	Thin exudative fibrin film and focal desquamation of mesothelial cells, less than 10 leukocytes per high-power field
3	Extensive fibrin exudation and diffuse desquamation of mesothelial cells, greater than 10 leukocytes per high-power field or focal microabscesses

**Table 2.** Leukocytes, C-reactive protein and peritonitis severity scores of rats

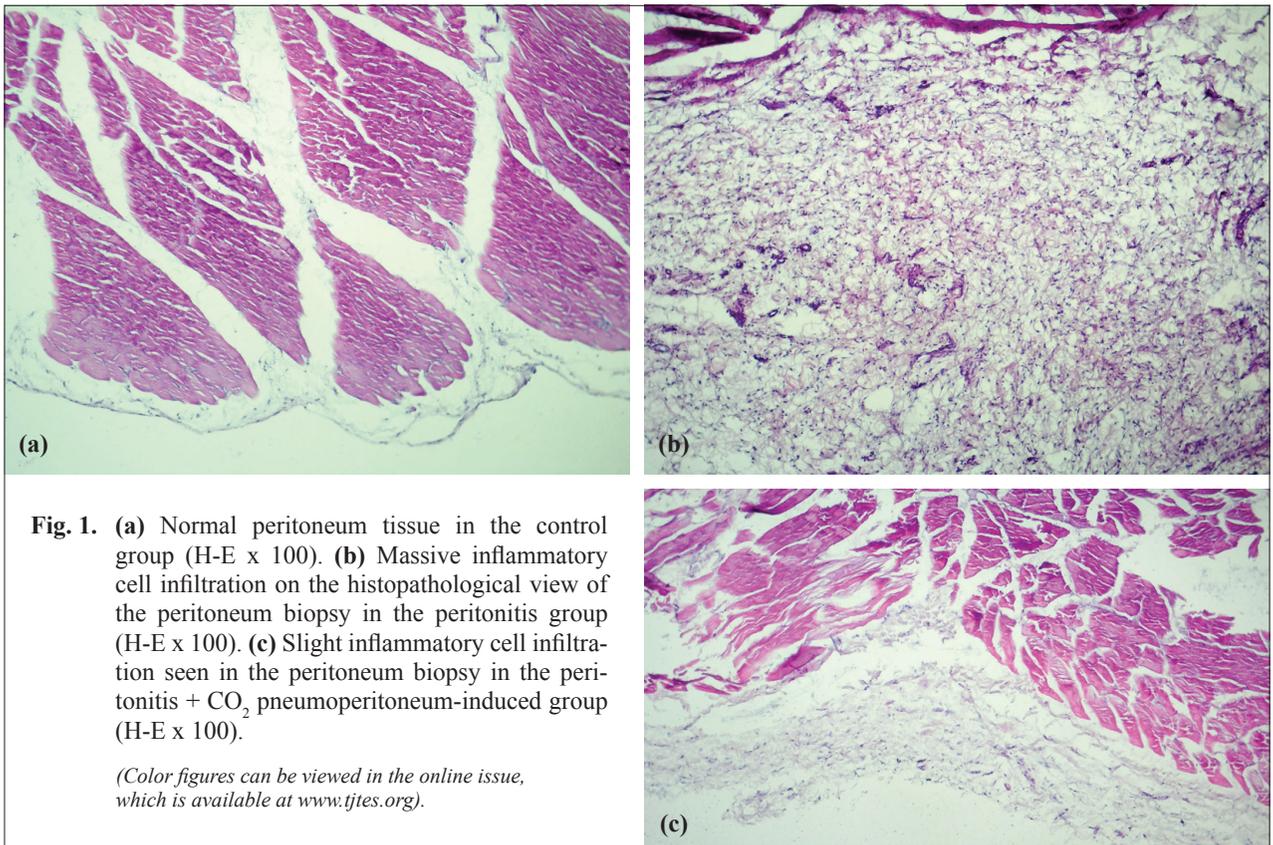
Groups	Leukocytes mean $\pm$ SD	CRP mean $\pm$ SD	Peritonitis severity mean $\pm$ SD
Group 1	419 $\pm$ 146	0.16 $\pm$ 0.05	0.42 $\pm$ 0.53
Group 2	918 $\pm$ 315	0.35 $\pm$ 0.12	2.7 $\pm$ 0.4
Group 3	716 $\pm$ 308	0.18 $\pm$ 0.11	1.5 $\pm$ 0.53

SD: Standard deviation.

## RESULTS

Leukocyte and CRP values and peritonitis severity scores of the rats are illustrated in Table 2. CRP and leukocyte values in the peritonitis-induced group and peritonitis+CO<sub>2</sub> pneumoperitoneum-induced group (Groups 2, 3, respectively) were found to be significantly higher than in the control group ( $p < 0.05$ ). When Groups 2 and 3 were compared, the values were found

to be significantly higher in the peritonitis+CO<sub>2</sub> pneumoperitoneum-induced group (Group 3) ( $p < 0.05$ ). The peritonitis severity scores were 0.4286 $\pm$ 0.53452, 2.7143 $\pm$ 0.46795 and 1.5714 $\pm$ 0.5352 in Groups 1, 2 and 3, respectively. The severity of peritonitis was significantly higher in the control group than in Groups 2 and 3 ( $p < 0.05$ ). The severity of peritonitis was lower in the peritonitis+CO<sub>2</sub> pneumoperitoneum-induced



group compared to the peritonitis-induced group ( $p < 0.05$ ) (Fig. 1).

## DISCUSSION

The results of our study demonstrated that CO<sub>2</sub> pneumoperitoneum does not have a negative effect on the severity of peritonitis in the presence of peritonitis induced with *E. coli*, even though it was observed that CO<sub>2</sub> pneumoperitoneum causes a lower inflammatory response and a lower increase in the severity of peritonitis.

In the clinical and experimental studies about peritonitis, the severity of inflammatory reaction against the peritonitis was evaluated by acute phase parameters such as the leukocyte count, CRP and histopathological investigations.<sup>[6,10,14,35,36]</sup>

In our study, in which these parameters were used, the total leukocyte count was observed to be significantly higher in the peritonitis-induced group than in the control group. However, the leukocyte count was significantly lower in the peritonitis and pneumoperitoneum-induced group in comparison with the sepsis group. The leukocyte count being significantly lower in the CO<sub>2</sub> pneumoperitoneum group compared to the peritonitis group showed that the CO<sub>2</sub> pneumoperitoneum caused a reduction in the severity of the infection in rats with peritonitis. Ure et al.<sup>[37]</sup> carried out an experimental study without inducing peritonitis and reported that the leukocyte counts in the 2nd and 48th hours were found to have increased in the laparotomy group in comparison with the CO<sub>2</sub> pneumoperitoneum group. In the same study, the leukocyte count was found to be significantly lower in the CO<sub>2</sub> pneumoperitoneum group compared to the air pneumoperitoneum group. This result led to the suggestion that the less severe leukocytosis in peritonitis depends on the direct effect of CO<sub>2</sub>, rather than on intraperitoneal pressure increase or turbulences produced by insufflations. The results from some studies with regard to the bacteriostatic and bactericidal efficacy of CO<sub>2</sub> support our view.<sup>[38-41]</sup>

In our study, the finding of a lower CRP value in the peritonitis+CO<sub>2</sub> pneumoperitoneum group than in the peritonitis group showed that CO<sub>2</sub> pneumoperitoneum decreased the acute phase inflammatory response against peritonitis. Similar to our results, Are et al.<sup>[40]</sup> also demonstrated with their experimental studies that CO<sub>2</sub> pneumoperitoneum decreased the acute phase inflammatory response against peritonitis. It has been demonstrated by *in vitro* studies that CO<sub>2</sub> pneumoperitoneum suppresses the metabolic response of leukocytes and lowers peritoneal macrophage activity, which also support our study results.<sup>[37,42,43]</sup> In a study researching the effect of CO<sub>2</sub> pneumoperitoneum on peritonitis in peritonitis-induced rats, similar

to our study, 1 ml of *E. coli* suspension was administered within the peritoneal cavity and interleukin (IL)-6 and CRP values were measured to evaluate the inflammatory response. It was observed that these values were significantly low in the CO<sub>2</sub> pneumoperitoneum-induced group, and it was reported that CO<sub>2</sub> pneumoperitoneum reduces inflammatory response in the peritoneum in the case of sepsis, when compared to open surgery.<sup>[22]</sup> In another study on pigs, it was found that the increase in the leukocyte and macrophage percentage was significantly low. Besides the low inflammatory response, it was observed that CO<sub>2</sub> pneumoperitoneum does not promote the bacteriemia or produce metabolic and hemodynamic problems in acute peritonitis.<sup>[37]</sup>

The results obtained in our study and the data reported in the literature showed that CO<sub>2</sub> pneumoperitoneum augments the severity of inflammatory response and peritonitis, and this was related to the effect of CO<sub>2</sub> gas, rather than the direct effect of pneumoperitoneum. The reason for CO<sub>2</sub> pneumoperitoneum reducing the severity of bacteriemia was attributed to the bacteriostatic and bactericidal effect of CO<sub>2</sub> itself.<sup>[14,28,36,40]</sup> Gill et al.<sup>[11]</sup> demonstrated the bactericidal and bacteriostatic effect of CO<sub>2</sub> on *E. coli*.

In our study, we determined that the severity score, evaluated by the biopsy of the peritoneum, was significantly lower in the peritonitis and CO<sub>2</sub> pneumoperitoneum group compared to the peritonitis group. İpek et al.,<sup>[14]</sup> having studied the effects of CO<sub>2</sub> pneumoperitoneum on the degree of bacteriemia and peritonitis, observed that 1 hour after cecostomy, peritonitis severity scores were higher in the CO<sub>2</sub> pneumoperitoneum group than in the control group, but 3 to 6 hours after cecostomy, there was no difference between the groups. Jacobi et al.,<sup>[22]</sup> in their experimental study investigating whether or not the laparoscopic interventions augment the bacteriemia and endotoxemia in the presence of peritonitis, reported that the laparoscopic interventions do not augment the bacteriemia and abscess processes.

In a study in which peritonitis in dogs was induced with *E. coli*, one of the groups was administered CO<sub>2</sub> via the intraperitoneal route, and compared with the other group, the investigators concluded that in peritonitis, the laparoscopic pneumoperitoneum does not stimulate the bacteriemia or worsen the metabolic or hemodynamic status.<sup>[33]</sup> In other studies, it was reported that CO<sub>2</sub> pneumoperitoneum did not increase the risk of endotoxemia or bacteriemia, compared to the laparotomy group,<sup>[44]</sup> and that the peritoneal macrophage activity was lower.<sup>[13]</sup> In a study that compared air and CO<sub>2</sub> pneumoperitoneum along with laparotomy, it was also reported that in the CO<sub>2</sub> pneumoperitoneum-induced group, the peritoneal macrophage activity was

low.<sup>[39]</sup> Both studies showed that CO<sub>2</sub> pneumoperitoneum reduced the inflammatory reactions.<sup>[13,39]</sup>

In an experimental study researching the effect of gas at the intraperitoneal site on the bacterial translocation and cytokine response, the reduction in the inflammatory response was attributed to the CO<sub>2</sub> gas.<sup>[44]</sup> Various studies have pointed out that the CO<sub>2</sub> gas exhibits a bacteriostatic and bactericidal effect, especially for the aerobic bacteria, and the reduction in the severity of bacteriemia in the CO<sub>2</sub> pneumoperitoneum was attributed to the same effect of CO<sub>2</sub>.<sup>[10,14,28,36,40]</sup>

Daphan et al.<sup>[45]</sup> evaluated the effects of laparotomy and CO<sub>2</sub> and air pneumoperitoneum on cellular immunity and peritoneal host defences in rats. They showed that laparotomy and air insufflation depressed cell-mediated immunity and peritoneal bactericidal activity. They concluded that CO<sub>2</sub> insufflation showed fewer detrimental effects on specific cellular immunity and local peritoneal host responses than air insufflation and laparotomy in experimental conditions.

Besides studies reporting that CO<sub>2</sub> pneumoperitoneum produces better results in rats with peritonitis compared to laparotomy, there are also studies suggesting the opposite. Bloechle et al.,<sup>[10]</sup> with their experimental studies in rats, reported that after the laparoscopy, the severity and location of bacteriemia and peritonitis increased when compared to the control group. Moreover, after the laparoscopy, a significant increase in the positive blood cultures was reported, in comparison with laparotomy. In another study, it was reported that the post-laparoscopy incidence of bacteriemia was higher; however, the systemic inflammatory response was slightly reduced.<sup>[38]</sup> The increase in the bacteriemia was attributed to the increase of lymphatic openings due to the increase in intraabdominal pressure, and therefore the transduction of peritoneal liquid into the systemic circulation.<sup>[10,46]</sup> We think that the results may be different since the design of that study was different from ours and other studies. While in our study, the peritonitis was induced by administering *E. coli* to all groups in equal quantity, in that study, in addition to uncontrolled quantities of other bacteria species, the chemical effects of stomach acid and intestinal content may have interfered in the process. In addition, there may be other factors that affected the severity of peritonitis. Likewise, there are studies that reported that the gas used to augment the severity of bacteriemia plays only a minor role.<sup>[47]</sup>

In conclusion, in the rats with peritonitis, the CO<sub>2</sub> pneumoperitoneum, compared to laparotomy, resulted in a less severe inflammatory response and peritonitis. Therefore, we think that in the cases of generalized peritonitis, surgical procedures for diagnosis and treatment can be carried out successfully, and that this

point will be highlighted more by randomized controlled clinical studies for the said purposes.

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