Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1347370
J Health Sci Med. 2023;6(5):1080-1086

The role of carbondioxide insufflation in preventing postoperative peritoneal adhesions in rats

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Cite this article as: Erdoğan C, Ayar I. Extra corporeal membrane oxygenation therapy in acute respiratory distress syndrome due to Coronavirus-2019 (COVID-19): a retrospective study. *J Health Sci Med.* 2023;6(5):1080-1086.

Received: 21.08.2023 ◆ **Accepted**: 12.09.2023 ◆ **Published**: 28.09.2023

ABSTRACT

Aims: Adhesion is the pathological connections that occur during the healing with scar formation of peritoneal surface defects. CO_2 is used the most frequently in laparoscopic operations for insufflation. It is believed that it causes to changes in the inflammatory reply of the pneumo-peritoneum, defects in acid-base balance and decrease in peritoneal macrophage functions. CO_2 is the only gas whose immunologic effects have been shown. It has been proven in experimental studies that the CO_2 insufflation causes to local peritoneal acidosis without affecting the systemic status. Moreover, it has also been shown that it decreases the pneumo-peritoneum TNF-α and IL-6 production; however, increases the IL-10 production which is an anti-inflammatory cytokine. In the literature, the relation between the laparoscopy and the postoperative adhesions has always been explained by taking the suggestion of its causing to less tissue trauma as a basis when compared with the open surgery. The inflammatory reply of the CO_2 has been less dealt with. In this study, we wanted to find the answer to the question whether the capno-peritoneum has a role in preventing the postoperative adhesion formation only by using CO_2 without a a laparoscopic operation.

Methods: 30 female Wistar Albino type rats whose weights varied between 250±20 were used in the study. The rats were divided into 5 groups. Each group had 6 rats. Rats were placed in standard polycarbon cages in groups of 6. The room temperature was kept in 21°C. The rats were fed with standard pellet food during the study and tap water was provided to them. The operational anesthesia was performed by injecting intramuscular Ketamine Hydrochloride (Ketalar, Parke Davis and Eczacıbaşı, İstanbul) 50 mg/kg and Xylazine hydrochloride (Rompun, Bayer HealthCare) 5 mg/kg.

Results: A meaningful difference ($p<0.05$) was determined between the inflammation results of the groups. The inflammation findings become lighter as moved from Group 1 to Group 5. A meaningful difference ($p<0.05$) was determined between the fibrosis results. The fibrosis findings become lower as moved from Group 1 to Group 5. A meaningful difference ($p<0.05$) was determined between the adhesion results of the groups. The adhesion findings become lower as moved from Group 1 to Group 5. A statistically meaningful difference was not determined ($p>0.05$) between the PAI values of the groups. A statistically meaningful difference was not determined ($p<0.05$) between the MDA values of the groups. The difference stems from Group 1 and Group 5. The MDA values of Group 1 is relatively higher than those of other groups; while the MDA values of Group 5 is found to be lower when compared with the other groups

Conclusion: Our results suggest that CO_2 pneumo-peritoneum has positive effects in postoperative intraperitoneal adhesion development. Since we formed a scraping model in our study, we cannot suggest that the adhesion formation is decreased with mechanical effect. The patho-physiological and molecular bases of the postoperative adhesion formation have been documented and described well. However, we consider that the capno-peritoneum and postoperative adhesion formation is prevented with anti-inflammatory effect. We need to conduct more studies to examine this mechanism.

Keywords: Postoperative adhesion, laparoscopy, capnoperitoneum

INTRODUCTION

Adhesion (being stick together) is the pathological connections that occur during the healing with scar formation of peritoneal surface defects. Adhesions may be congenital or acquired later. Congenital adhesions occur after the abnormal development of peritoneal cavity (vitello-intestinal bands etc.). Acquired adhesions are divided into two classes as inflammatory and postoperative. Inflammatory adhesions occur due to appendicitis, cholecystitis, diverticulitis, pelvic inflammatory disease, or after the use of intrauterine contraception devices.[1,2]

- When the physiopathology of adhesion formation is considered, the following situations are observed;
- Serosal damage,
- Increase in local inflammatory reply, increase in vascular permeability and inflammatory exudate,
- Formation of free radicals such as superoxide, peroxidase and hydroxyl radicals, and these formations causing to defects in cell membrane,
- Activation of the coagulation system (fibrin formation) and the fibrinolytic system (fibrinogen degradation)

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and the mechanisms that move one within the other during the formation of imbalance intraperitoneal adhesions that occur in the balance between these two elements[3-6]

Menzies reported that intraabdominal adhesion developed in 79% and 93% of the patients who received intraabdominal operational procedure is his study.[2] The major morbidities caused by intraabdominal adhesions are intestinal obstruction infertility, difficult and risky re-explorations, ectopic pregnancy and chronic stomachache. Laparoscopy technique is used widely in surgical practices.

Laparoscopic operations mean less trauma in the peritonea, less intraoperative bleeding, polite manipulations to intraabdominal organs and tissues, less tissue damage in areas other than the operation area, less exposure to glove powder, gauze, compress and operational tools, and postoperative earlier recovery. These characteristics make the laparoscopy technique superior to conventional surgical methods in terms of adhesion formation status.

Carbon dioxide (CO_2) is used the most frequently in laparoscopic operations for insufflation; and with its biological characteristics, it is still the most suitable gas in this field. It is believed that it causes to changes in the inflammatory reply of the pneumo-peritoneum, defects in acid-base balance and decrease in peritoneal macrophage functions. CO_2 is the only gas whose immunologic effects have been shown. It has been proven in experimental studies that the CO_2 insufflation causes to local peritoneal acidosis without affecting the systemic status. Moreover, it has also been shown that it decreases the pneumo-peritoneum TNF-α and IL-6 production; however, increases the IL-10 production which is an anti-inflammatory cytokine. In the literature, the relation between the laparoscopy and the postoperative adhesions has always been explained by taking the suggestion of its causing to less tissue trauma as a basis when compared with the open surgery. The inflammatory reply of the CO_2 has been less dealt with. In this study, we wanted to find the answer to the question whether the capno-peritoneum has a role in preventing the postoperative adhesion formation only by using CO_2 without a laparoscopic operation.

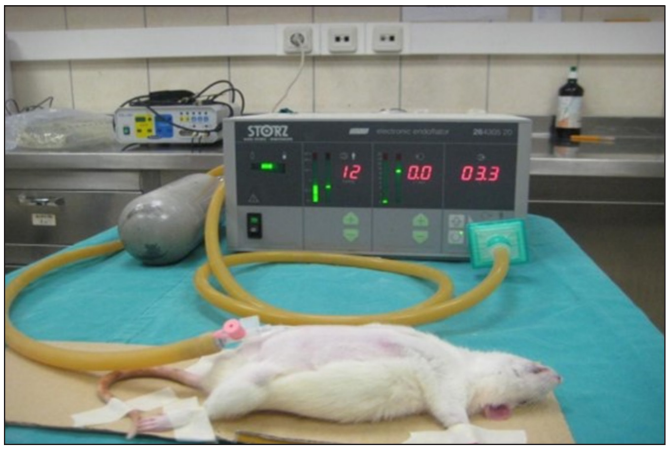
METHODS

This experimental study was carried out with the permission of Gazi University Animal Experiments Local Ethics Committee (Date: 04.09.2011, Decision No: B.30.2.GÜN.O.EU.00.00/38-5869.30). The study adhered to the animal research guidelines of the National Institute of Health.

30 female Wistar Albino type rats whose weights varied between 250±20 were used in the study. The rats were divided into 5 groups. Each group had 6 rats. Rats were placed in standard polycarbon cages in groups of 6. The room temperature was kept in 21°C. The rats were fed with standard pellet food during the study and tap water was provided to them. The operational anesthesia was performed by injecting intramuscular Ketamine Hydrochloride (Ketalar, Parke Davis and Eczacıbaşı, İstanbul) 50 mg/kg and Xylazine hydrochloride (Rompun, Bayer HealthCare) 5 mg/kg.

Operational Procedure

The necessary sterile conditions were provided after the anesthesia, and the rats were fixed to the operation board from their four extremities, and abdominal front walls of the rats were shaved and cleaned with povidone iodine. The cannula was connected to an electronic insufflator (Storz and Co., Tutthufen, Germany) and the CO_2 was insufflated so as it remained in 6 mmHg (**Picture 1**). After the operation, the rats were put in the cages in groups. The rats were then observed for 10 days in standard feeding and living conditions. Tissue samples were collected and frozen with liquid nitrogen, and kept in -80 °C until the analysis time.



Picture 1. CO_2 was insufflated so as it remained in 6 mmHg

Groups

Group I: The Sham Group (n: 6): Laparotomy was performed from the middle line, and closed without any interventions with 3/0 vicril.

Group II: The Control Group (n: 6): Laparotomy was performed from the middle line, and the petechial bleedings were performed with sterile dry sponge over the cecum, and the ileo-cecal artery was clamped for 1-2 minutes to form the scraping model. After this process, the incision was closed with 3/0 vicril.

Group III (n: 6): Laparotomy was performed from the middle line after 15 minutes carbon dioxide insufflation. Then petechial bleedings were performed with sterile dry sponge over the cecum, and the ileo-cecal artery was

clamped for 1-2 minutes to form the scraping model. After this process, the incision was closed with 3/0 vicril.

Group IV (n: 6): Laparotomy was performed from the middle line after 15 minutes carbon dioxide insufflation. Then petechial bleedings were performed with sterile dry sponge over the cecum, and the ileo-cecal artery was clamped for 1-2 minutes to form the scraping model. After this process, the incision was closed with 3/0 vicril. Then carbon dioxide insufflation was performed for 45 minutes.

Group V (n: 6): Laparotomy was performed from the middle line. Then petechial bleedings were performed with sterile dry sponge over the cecum, and the ileo-cecal artery was clamped for 1-2 minutes to form the scraping model. After this process, the incision was closed with 3/0 vicril. Then carbon dioxide insufflation was performed for 45 minutes.

Parameters

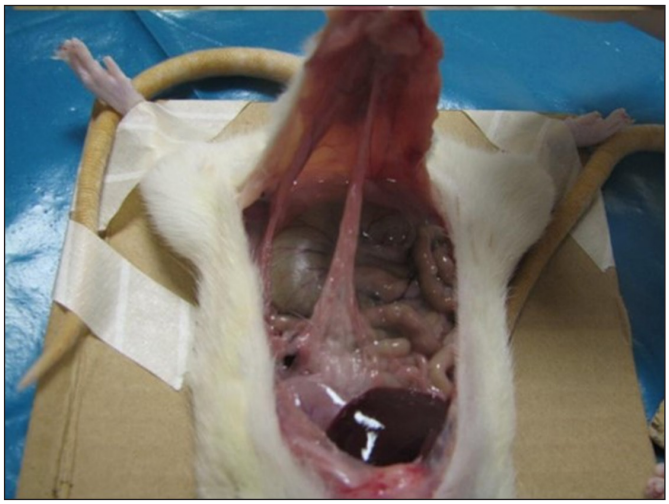
Tissue rat malondialdehyde (MDA) level measurement: The quantitative measurement of the MDA was performed with the ready-made Csabio ® tPA (American Diagnostica Inc.) kit according to the introductions of the producer company with the ELISA (Enzyme Linked-Immuno-Sorbent Assay) method. The values recorded were as pg/ml.

Tissue plasminogen activator inhibitor-1 (PAI-1) level measurement: To measure the amount of the Plasminogen activator inhibitor-1 quantitatively, the Cusabio® Plasma PAI-1 (American Diagnostica Inc.) ready-made kit was used according to the introductions of the producer company with the ELISA (Enzyme Linked-Immuno-Sorbent Assay) method. The values were recorded as pmol/ml.

Intraabdominal adhesion scoring: After 10 days, the rats were anesthetized with 75 mg /kg ketamine hydrochloride. An incision with the shape of a reverse-U was performed in the front wall of the abdomen to obtain a better vision, and all the adhesions in the abdomen were examined, recorded and classified (Picture 2). The Mazuji Classification was used in macroscopic classification.[7] The formed adhesions were taken out without damaging them, and put in 10% formalin solution, and sent to the Gazi University Faculty of Medicine Pathology Department for histopathological assessment. Some tissue samples were also sent to the biochemistry laboratory for MDA and PAI level measurements. After the exemplification, the rats were sacrificed under anesthesia by taking intracardiac blood and hypotensive collapse.

Histopathological Examination

The specimens, dehydrated and embedded in paraffin, were dyed with H&E in 1 mm thickness, and assessed in light microscope in terms of fibrosis and inflammation (Table 1,2). The fibroblast cell density (Table 1) and inflammation scoring systems (Table 2) were used in histopathological examination.[8]



Picture 2. Limited adhesion in an area thick (group 2 adhesion)

Table 1. Macroscopic adhesion evaluation scoring (Mazuji et al.)

Score	Evalution
0	No fibrosis
1	Minimally, loose
2	Moderate
3	Fluoride,intense

Table 2. Fibrosis assessment scoring (Hooker et al.)

Score	Evaluation
0	Not inflammation
1	Giant cells, scattered mononuclear inflammatory cells (Chronic inflammation)
2	An increased number of giant cells mixed with lymphocytes, neutrophils, eosinophils plasma cells (acute inflammation)
3	Many mixed inflammatory cells, presence mikroapse (acute suppurative inflammation)

Statistical Analysis

he data were entered into the SPSS 11.0 package program. In determining the difference between the groups, the Kruskal-Wallis variance analysis was used; and in determining the groups with the differences, the Mann-Whitney U non-parametric test was used. The $p<0.05$ value was accepted as statistically meaningful. The averages were given as average±standard deviation.

RESULTS

A meaningful difference ($p<0.05$) was determined between the inflammation results of the groups. The inflammation findings become lighter as moved from Group 1 to Group 5 (Table 3). A meaningful difference ($p<0.05$) was determined between the fibrosis results. The fibrosis findings become lower as moved from Group 1 to Group 5 (Table 4). A meaningful difference ($p<0.05$) was

determined between the adhesion results of the groups. The adhesion findings become lower as moved from Group 1 to Group 5 (Table 5). A statistically meaningful difference was not determined (p>0.05) between the PAI values of the groups. A statistically meaningful difference was not determined (p<0.05) between the MDA values of the groups. The difference stems from Group 1 and Group 5. The MDA values of Group 1 is relatively higher than those of other groups; while the MDA values of Group 5 is found to be lower when compared with the other groups.

Table 3. Comparison of the rate of inflammation between groups

Group	Inflammation				P value
	0 n (%)	1 n (%)	2 n (%)	3 n (%)	
1	-	-	-	6 (100)	0.0001
2	-	-	6 (100)	-	
3	-	4 (66.7)	2 (33.3)	-	
4	-	6 (100)	-	-	
5	4 (66.7)	2 (33.3)	-	-	

Table 4. The comparison between groups fibrosis

Group	Fibrosis			P value
	0 n (%)	1 n (%)	2 n (%)	
1	-	1 (16.7)	5 (83.3)	0.0001
2	-	5 (83.3)	1 (16.7)	
3	-	3 (50.0)	3 (50.0)	
4	-	6 (100)	-	
5	6 (100)	-	-	

(%)*: Row percent, Kruskall Wallis Test was used.

Table 5. Comparing the adhesion between groups

Group	Adhesion				P value
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	
1	-	2 (33.3)	2 (33.3)	2 (33.3)	0.022
2	-	1 (16.7)	2 (33.3)	3 (50.0)	
3	1 (16.7)	3 (50.0)	2 (33.3)	-	
4	1 (16.7)	4 (66.7)	1 (16.7)	-	
5	2 (33.3)	3 (50.0)	1 (16.7)	-	

(%)*: Row percent, Kruskall Wallis Test was used.

A statistically meaningful difference was not determined (p>0.05) between the PAI values of the groups. A statistically meaningful difference was not determined (p<0.05) between the MDA values of the groups. The difference stems from Group 1 and Group 5. While the MDA values of Group 1 are relatively higher than those of other groups, the MDA values of Group 5 are found to be lower than those of other groups. A positive linear relation in medium level was determined between the PAI and MDA values (correlation coefficient: 0,381, p<0.05). As the PAI values increase, so do the MDA values. As the inflammation findings become severe, so do the severeness of fibrosis findings. A positive linear relation in medium level was determined between the inflammation findings and MDA values (correlation coefficient: 0,382, p<0.05). As the inflammation findings become severe, the MDA values increase. A strong positive linear relation was determined between the fibrosis findings and PAI values (correlation coefficient: 0,513, p<0.05). As the fibrosis findings become severe, the PAI values increase. A positive linear relation in medium level was determined between the fibrosis findings and MDA values (correlation coefficient: 0,399, p<0.05). As the PAI values increase, so do the MDA values. As the fibrosis findings become severe, the MDA values increase. A positive linear relation in medium level was determined between the adhesion findings and PAI values (correlation coefficient: 0,324, p<0.05). As the PAI values increase, so do the MDA values. As the adhesion findings become severe, the PAI values increase (Table 6).

DISCUSSION

Peritoneal adhesions occur after the single-layered mesothelial cells that form the peritonea are harmed due to some reasons (mechanical, ischemic, chemical, infective, inflammatory, etc.).

Table 6. Inflammation, fibrosis, adhesion, PAI 1 and MDA value relationship between

	Inflammation	Fibrosis	Adhesion	PAI	MDA
Inflammation					
Correlation composition (tau)	1	0.454*	0.193	0.111	0.382*
n	30	30	30	30	30
P	.	0.005	0.238	0.433	0.007
Fibrosis					
Correlation composition (tau)	0.454*	1	0.193	0.513*	0.399*
n	30	30	30	30	30
P value	0.005	.	0.238	0.0001	0.007
Adhesion					
Correlation composition (tau)	0.294	0.193	1	0.324*	0.051
n	30	30	30	30	30
P	0.114	0.238	.	0.024	0.719

The general incidence of re-application to the hospital due to adhesion when compared with operation procedures was reported as 4.6%.[9,10]

Various models such as damaged uterus horn model, peritonea damage model, colon anastomose model, ileal transection model, bacterial peritonitis model and clamping model were formed for experimental adhesion examination purposes. The clamping model that is applied in our study is proper for its defects being two-staged. The first stage is forming mechanical serosal intestine wall damage with direct sponge application; the second stage is forming ischemic damage after the vein is clamped. The reasons for our preference of this model is due to its similarity to surgical methods in the abdomen.

We did not determine a statistically meaningful difference among the inflammation results, the adhesion results and the fibrosis results in groups. We found that the inflammation findings became less severe as moved from Group 1 to Group 5. We found that the fibrosis findings became less severe as moved from Group 1 to Group 5. We also found that the adhesion findings became less severe as moved from Group 1 to Group 5. The findings of the study conducted by Scott-Coombes et al.[11] support our findings. In their studies, they determined PAI-1 in high density in peritoneal tissues of the patients with adhesion. We did not determine a statistically meaningful difference between the PAI-1 values among the groups in our study. We did not determine a statistically meaningful difference between the MDA values in groups. The difference stems from Group 1 and Group 5. The MDA values of Group 1 is higher than those of other groups, while the MDA values of Group 5 are lower than those of other groups. As the PAI-1 values increase, so do the MDA values. As the inflammation findings become severe, so do the severeness of fibrosis findings. As the inflammation findings become severe, the MDA values increase. As the fibrosis findings become severe, the PAI-1 values increase. As the fibrosis findings become severe, the MDA values increase. As the adhesion findings become severe, the PAI-1 values increase. As the adhesion findings in Group 1 become severe, the PAI-1 values increase. As the adhesion findings become severe in Group 3, the MDA values decrease. No relation was determined among the other findings and values in other groups.

The history of laparoscopy dates back to one century ago.[12] In early 1900s, endoscopy was used mainly in bladder, rectum, larynx, esophagus examinations; in 1901, a Russian Gynecologist named Dimitri Von Ott reported that he had entered to the peritoneal cavity with a minimal incision and examined the inside of the abdomen, and this process was later called as Ventroscopy by him.[13,14]

Laparoscopy is related with a small entry and manipulation injuries; however, pneumo-peritoneum is also responsible for the decrease in acute phase reply.[15] Laparoscopic surgery in abdominal explorations ensures that the blind dissection and retractors and compresses are used less. Moreover, when compared with traditional surgery, it decreases the washing and drying of peritonea, and contact of operational objects, tissue damage, and bleeding in operational area.[16,17] For these reasons, it is possible to suggest that laparoscopy causes to less adhesion. Carbon dioxide is the most frequently used gas in today's world.[18] The advantage of carbon dioxide is that it is not inflammable and explosive; its diffusion to the tissues is fast, and it is relatively cheaper. Gas embolism is the most important complication of the gasses that are used for pneumo-peritoneum. A gas such as carbon dioxide that is absorbed fast causes less persistent airway obstructions in right ventricular outlet. The most important disadvantage of carbon dioxide is that it dissolves in solutions quickly; and its causing to unwanted biological effects such as hypercapnia and acidosis less.[19] However, these effects are in minimal level in people who do not have further stage respiration problems and cardiac pathology. For these reasons, carbon dioxide is the most frequently preferred gas today. CO_2 is known to change the systemic immune reply in a proper way during laparoscopic surgery of the pneumo-peritoneum. It has been proven that CO_2 insufflations cause to local peritoneal acidosis. CO_2 is a strong anti-inflammatory agent.[20-22] It has been proven that CO_2 decreases the systemic inflammatory reply and capno-peritoneum macrophage function.[22,23] In case the peritoneal pH decreases to 6,1 after the CO_2 insufflation, the macrophage intracellular pH values also decrease.[24] It has been shown that superoxide production as well as phagocyte and cytokines are suppressed with the decrease in intracellular pH.[25,26] The decreasing pro-inflammatory cytokine production after the laparoscopy in peritoneal tissues may be responsible for the decrease in postoperative pain and adhesion formation.[25-27]

Adhesion formation is a complicated process. Macrophages, fibroblasts and mesothelial cells have major roles in the stages of adhesion formation. The studies conducted so far have shown that there is a dynamic balance between the pro- and anti-inflammatory cytokines in these stages of adhesion formation.[28,29] Surgery, inflammation and other similar factors cause to the collapse of this balance. It is known that when to defective sides come together, intraperitoneal adhesion formation is triggered. Miyano et al.[30] and Jansen et al.[31] reported that CO_2 insufflation and the mechanical effect of the pneumo-peritoneum decrease the contact between the defective sides. They determined that PAI-1 concentrations increased in the laparoscopic group as

a secondary process to the CO_2 insufflation.[32,33] In our study, as the severeness of the inflammation and fibrosis increased, so did the PAI-1 concentration.

Miyano et al.[30] reported that CO_2 insufflation decreased the contact between the damaged surfaces. It was suggested that this was due to the increase in the pressure after the pneumo-peritoneum duration and insufflation pressure causing to an increase in adhesion in hypoxia.[33,34]

Corona et al.[35] conducted a study and reported that adhesion and inflammation increased in CO_2 models. Unlike this study, it was determined in our study that capno-peritoneum decreased the adhesion and inflammation especially in the long-term group.

We did not observe a clinical side effect or histopathological abnormality due to CO_2 in our study and this result supports the findings of Miyano et al.[30] Bustorff-Silva et al.[36]

CONCLUSION

Our results suggest that CO_2 pneumo-peritoneum has positive effects in postoperative intraperitoneal adhesion development. Since we formed a scraping model in our study, we cannot suggest that the adhesion formation is decreased with mechanical effect. The patho-physiological and molecular bases of the postoperative adhesion formation have been documented and described well. However, we consider that the capno-peritoneum and postoperative adhesion formation is prevented with anti-inflammatory effect. We need to conduct more studies to examine this mechanism.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gazi University Animal Experiments Local Ethics Committee (Date: 04.09.2011, Decision No: B.30.2.GÜN.O.EU.00.00/38-5869.30).

Informed Consent: This experimental animal study does not require informed consent.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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