

The Influence of Carbon Dioxide Pneumoperitoneum on Systemic Inflammatory Response Syndrome and Bacterial Translocation in Patients With Bacterial Peritonitis Caused by Acute Appendicitis

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Abstract

Objective. To explore the influence of carbon dioxide pneumoperitoneum (CDP) on system inflammatory response syndrome (SIRS) and bacterial translocation (BT) in patients with bacterial peritonitis (BP) caused by acute appendicitis (AA). **Methods.** Eighty-six consecutive subjects were randomly divided into the laparoscopy and laparotomy groups ($n = 44$ and $n = 42$, respectively). The levels of white blood cells (WBC), C-reactive protein (CRP), tumor necrosis factor α (TNF- α), and interleukin 6 (IL-6) of the 2 groups were tested preoperatively and at days 1, 2, and 4 after surgery. Blood and secretion culture was performed to verify whether septicemia or incision infection occurred, respectively. And the abdominal ultrasound or computed tomography scanning was used to diagnose peritoneal abscess for the suspected patients. The essential risk factors related to the aggravation of SIRS were analyzed through analysis of variance and binary logistic regression. **Results.** The postoperative blood levels of WBC, CRP, TNF- α , and IL-6 on day 4 in the laparoscopy group were significantly lower than those in the control group (all P s $< .05$). The differences in incidence rates of septicemia and peritoneal abscess between the CDP and control groups were not statistically significant ($P > .05$). Nevertheless, the incision infection rate in the laparoscopy group was apparently lower than that in the control group (4.55% vs 19.04%, $P = .047$). Analysis of variance and binary logistic regression showed that the non-pneumoperitoneum, pathological type of appendicitis, and multidrug resistant infections were the 3 major risk factors for SIRS (the P values were .001, .019, and .012, respectively). **Conclusion.** It was found that CDP is safe for BP and could be a potential protective factor to mitigate BP effectively, indicating that the performance of laparoscopy operation under CDP is feasible to control SIRS; at the same time, CDP would not raise the incidence rate of BT.

Keywords

carbon dioxide pneumoperitoneum, bacterial peritonitis, system inflammatory response syndrome, bacterial translocation

Introduction

Carbon dioxide pneumoperitoneum (CDP) can provide a sufficiently physical room for laparoscopy. However, due to the rapid diffusion, absorption and expulsion of CO₂ in the abdominal cavity, high concentration of CO₂ will not only apparently increase the intra-abdominal pressure,^{1,2} which will not only cause splanchnic ischemia^{3,4} but also reduce macrophage cytokine secretion and phagocytic activity.⁵ The biological effect of CDP on the abdominal cavity and its pathophysiological effect on the whole body should not be neglected.

Bacterial translocation (BT) has been defined as the movement of viable enteric bacterial to the mesenteric

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lymph nodes (MLNs) and distant organ sites such as the liver and spleen. This definition was initially described by Berg et al⁶ and Deitch et al.⁷ BT could lead to the aggravation of abdominal infection (AI) and is a potential triggering factor for septicemia and multiple organ dysfunction syndrome (MODS).⁸ On account of pressure propagation, pH change and other factors, CDP can result in BT in patients or animal models with bacterial peritonitis (BP), thus complicating the treatment of peritonitis treated with laparoscope.⁹

As an inflammatory disease that can cause AI, acute appendicitis (AA) could lead to peritonitis by the way of inhibiting the enzyme system and impairing optimal macrophage functioning. However, the effect of CO₂ pneumoperitoneum is still controversial. Evrard et al¹⁰ found no change in macrophage function after CO₂ pneumoperitoneum,³ whereas Collet et al¹¹ demonstrated that macrophage function may actually be increased after insufflation. It remains unclear whether CDP aggravates AI caused by AA. Therefore, this study aimed to explore this question. We observed 86 patients with BT who underwent CDP laparoscope or traditional laparotomy. The differences in the inflammation indexes and BT after operation between laparoscopy and laparotomy were compared to evaluate the safety and validity of CDP for patients with abdominal infection. The processes are reported as follows.

Materials and Methods

Patients

From January 2016 to January 2017, we studied, in a prospective randomized study, 86 patients consecutively (53 men and 33 women) with BP caused by AA. Patients were randomly assigned to be treated with laparoscopy (the laparoscopy group, *n* = 44, consisting of 26 males and 18 females) or laparotomy (the control group, *n* = 42, consisting of 27 males and 15 females), according to a computer-generated table of random numbers. Randomization was performed by a research assistant. The subjects are numbered from 1 to 90 according to the order of hospitalization. Subsequently, the research assistant randomly assigned the virtual subjects into 2 groups at 1:1 ratio with a computer-generated table of random numbers. Patients and the surgeons were informed about the type of operation methods just before the intervention. The research assistant did not anticipate the inclusion of subjects. During the study, 4 subjects (1 in laparoscopy group, 3 in laparotomy group) were excluded for the negative culture of abdominal exudates. The study protocol was approved by the Ethical committee of the Shantou Central Hospital, and informed consent was obtained for every patient.

The subjects who suffered from BP (BP) caused by AA were screened based on the following standards⁹: (a)

Inclusion criteria: a definite diagnosis of AA; onset of AA from 24 to 72 hours; suffered from systemic inflammatory response (SIRS) before operation; SIRS was defined using American College of Chest Physicians (ACCP) recommendations criteria. That is, patients were considered to have SIRS if they met 2 or more of the following conditions: (1) temperature ≥ 38 or $\leq 36^\circ\text{C}$, (2) heart rate ≥ 90 beats/min, (3) respiratory rate ≥ 20 breaths/min or PaCO₂ ≤ 32 mm Hg, and (4) white blood cell (WBC) count $\geq 12\,000$ or $\leq 4\,000/\text{mL}$, or presence of more than 10% immature neutrophils^{12,13}; and the culture of abdominal exudates was positive. (b) Exclusion criteria: patients with major organ dysfunction and children or elderly patients and the culture of abdominal exudates was negative. The differences among patients in age, gender, body mass index (BMI), the course of the disease, the preoperative levels of WBC, C-reactive protein (CRP), tumor necrosis factor α (TNF- α), and interleukin 6 (IL-6), pathological types of appendix, whether perforation, duration of operation, anesthetic ways, hospitalization, total cost, and American Society of Anesthesiologists (ASA) grade were not statistically significant between the groups (all *P*s > .05, Table 1).

Operations

Operation performed by the same surgeons. The control group was given a routine operation by laparotomy, whereas the laparoscopy group was given CDP via laparoscope. Operative routes via 3 openings and the left tilt position of Trendelenburg were undertaken through general anesthesia¹⁴ (Figure 1). To observe the appendix and its surroundings, a 10-mm-wide incision in the superior margin of the umbilicus was made. Based on this incision, CDP was established with a pressure of 12 mm Hg, and a 10-mm trocar was inserted to explore the abdominal cavity. The opposite McBurney point and the one-third lower middle between the umbilicus and mons pubis were chosen as the main operating and auxiliary holes with two 3-mm trocars, respectively. When locating the appendix, the adhesin connecting appendix with its surrounding tissue was separated. The apex or mesoappendix was gripped, and the vessels of the mesoappendix were subsequently cut off by using an ultrasound knife. Separating of appendix was continued until the root was found and ligated. The appendix was put into a specimen bag and removed through the main operating hole.¹⁵ The drainage tubes of the abdominal cavity were selectively placed according to the severity of the appendicitis.

Observational Indexes

The levels of WBC, CRP, TNF- α , and IL-6 were detected at 4 time points: preoperation, day 1, 2, and 4 after

Table 1. The Basic Data of the 2 Groups.

Clinical Factors	Laparoscopy Group (n = 44)	Control Group (n = 42)	t / χ^2 / z	P (Exact Significance [2-Sided])
Age (years)	46 ± 14.5	43 ± 13.3	0.999	.321
Sex (n)			0.245	.620
Male	26	27		
Female	18	15		
BMI (kg/m ²)			0.501	.479
≥30	19	15		
<30	25	27		
Course of disease (n)			1.119	.290
<48 h	28	22		
72 h > course of disease > 48 h	16	20		
Inflammatory factor (pre)				
WBC (×10 ⁹ /L)	15.5 ± 1.6	15.7 ± 1.4	-0.616	.540
CRP (mg/L)	69.5 ± 5.8	70.6 ± 4.2	-1.003	.319
TNF- α (pg/mL)	91.3 ± 18.4	92.0 ± 10.1	-0.217	.829
IL-6 (pg/mL)	226.1 ± 34.2	225.9 ± 28.4	0.029	.977
Pathological type				.445
AGA	5	2		
ASA	33	34		
APA	6	6		
Multidrug resistant				.479
Yes	3	5		
No	41	37		
Perforation			-	0.683
Yes	3	2		
No	41	40		
Operative time (min)	53.3 ± 11.2	47.9 ± 14.2	1.963	.053
Anesthesia			-1.794	.073
General anesthesia	44	39		
Spinal anesthesia	0	3		
Hospitalization (days)	4.2 ± 1.0	4.5 ± 0.8	-1.532	.129
Total cost (1000¥)	7.3 ± 1.5	6.5 ± 1.8	2.243	.028
American Society of Anesthesiologists grade			-0.424	.672
I	40	37		
II	4	5		
III	0	0		

Abbreviations: BMI, body mass index; WBC, white blood cells; CRP, C-reactive protein; TNF- α , tumor necrosis factor α ; IL-6, interleukin-6; AGA, acute gangrenous appendix; ASA, acute suppurative appendix; APA, acute perforative appendix.

operation. A blood culture at the first hour and third day after operation was performed to determine septicemia, secretion culture was done to evaluate the incision infection, and the abdominal ultrasound or computed tomography (CT) scanning was used to diagnose peritoneal abscess for the suspected patients.

Statistical Analysis

The repeated-measures analysis of variance (ANOVA) was applied to compare the same factors on different days. The chi-square test was used to analyze the rates of count

data. Binary logistic regression was applied to screen the factors that might aggravate SIRS. The statistical software package SPSS 17.0 was applied for the data analysis, and statistical significance was claimed when $P < .05$.

Results

The laparoscopy group required several minutes longer operating time than the laparotomy group (Table 1) and hospitalization was shorter for laparoscopy group, but not statistically significant (Table 1). In the laparoscopy group, conversion was not required.

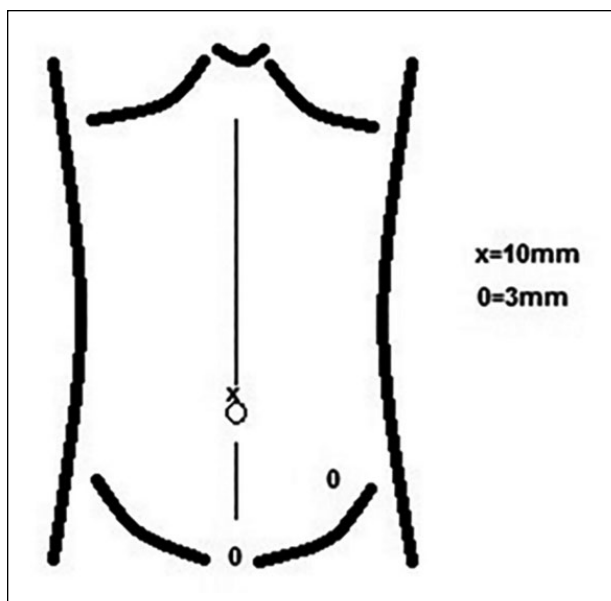


Figure 1. Schematic position of 3- and 10-mm portals.

Changes of the Inflammation Cytokines

The levels of WBC, CRP, TNF- α , and IL-6 in the laparoscopy group declined steadily and returned to near baseline by day 4 after operation. The differences between preoperation and day 4 after operation were statistically significant ($P < .05$, Figure 2A-D). However, the levels of WBC, CRP, TNF- α , and IL-6 in the control group were almost higher on day 2 than those before operation, though with a decline observed from the second day after operation. The levels of WBC, CRP, and IL-6 in the control group on day 4 after operation were significantly lower than those observed preoperation ($P < .05$), but TNF- α was not ($P > .05$). The levels of WBC, CRP, IL-6, and TNF- α in the laparoscopy group on day 4 after operation were significantly lower than that at preoperation ($P < .05$, Figure 2A-D).

The levels of WBC, CRP, TNF- α , and IL-6 on the day 4 in the laparoscopy group were statistically significantly ($P < .05$, Figure 1A-D) lower than those in the control group.

Complications Resulting From BT

The differences in the incidence rates of septicemia and peritoneal abscess between the laparoscopy and control group were not statistically significant ($P > .05$, Table 2). Nevertheless, the incision infection rate in the laparoscopy group was apparently lower than that in the control group (4.55% vs 19.04%, $P = .047$, Table 2).

There were 0 and 2 cases of septicemia (blood culture positive) in the laparoscopy and control group, respectively, and the difference between the groups was not

significant ($P = .236$, Table 2). There were 1 and 4 cases of peritoneal abscess in the laparoscopy and control group, respectively, and the difference between the groups was not significant ($P = .197$, Table 2). There were 2 and 8 cases of incision infection in the laparoscopy and control groups, with infection rates of 4.55% vs 19.04%, respectively, and the difference between the groups was significant ($P = .047$, Table 2).

Binary Logistic Regression

The suspected risk factors associated with the aggravation of SIRS are listed in Table 3, including pneumoperitoneum, age, body mass index, course of disease, appendix pathology, multidrug resistant infection, duration of operation, anesthesia, incision length, number of incisions, usage of specimen bags, and the grade of WHO Pain Grade System (WPGS) on the first postoperative day. Through ANOVA, it was found that non-pneumoperitoneum, gangrenous appendicitis, multiple drug-resistant infections, over 1-hour duration of operation, over 1-cm incision length were statistically significant with the aggravation of SIRS ($P = .001$, .020, .007, .047, and .014, respectively, Table 3). A further analysis of binary logistic regression among the above 5 factors showed that non-pneumoperitoneum, gangrenous appendicitis, and multidrug resistant infections were statistically significant ($P = .001$, .019, and .012, respectively, Table 4).

Discussion

About SIRS

When an organism suffers from excessive stress reactions or disorders, the microorganism and/or its toxin parasitizing in the intestinal tract and/or antigen products would penetrate the barrier of the intestinal mucosa and subsequently invade the previously aseptic intestinal tissue, such as the placenta percreta of intestinal wall, the lymphoglandulae mesentericae, portal system, and other distant organs. This process is called bacterial translocation (BT), which might lead to intestinal infection, and trigger SIRS or even cause MODS.¹⁶

Bacterial peritonitis (BP) could stimulate the organism to induce an excessive immune response, resulting in SIRS, which could develop into MODS and even lead to death. CD4⁺ T lymphocytes play an important role in the processes of anti-microorganism and mediate humoral immunity. Once the level of humoral immunity decreases, the organism's capability of anti-infection is destroyed. The weakened immunity would cause organism inflammation, disturb the balance of anti-inflammation cytokines and activate intestinal epithelial cells (IECs). The excessively active IEC would secrete TNF- α and IL-1, increase

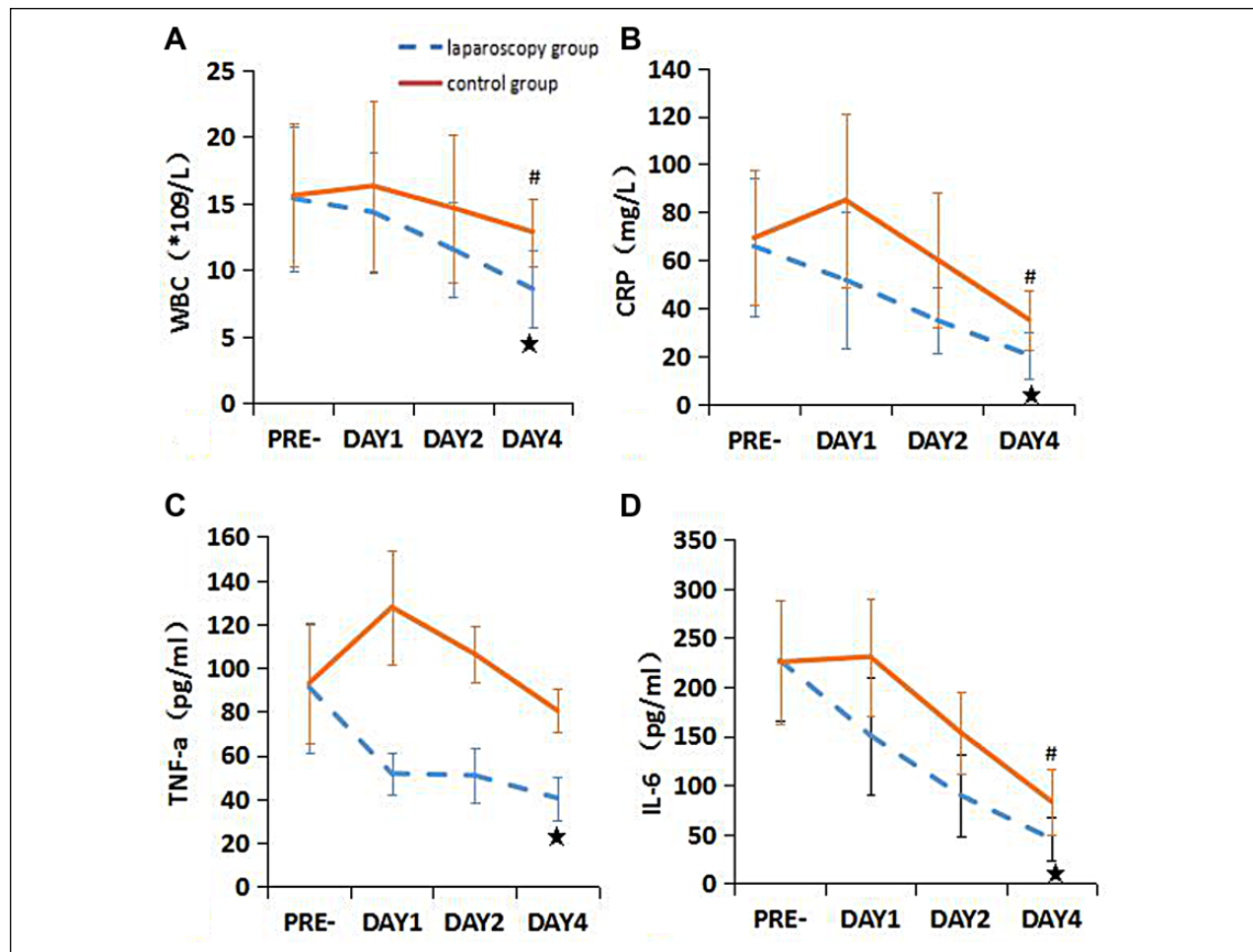


Figure 2. The pre- to postoperative change of inflammatory factor in the 2 groups.

Table 2. Comparison of Complications Caused by Bacterial Translocation Between the 2 Groups.

Parameters	Laparoscopy Group (n = 44)	Control Group (n = 42)	P (Exact Significance [2-sided])
Septicemia	0	2 (4.76%)	.236
Peritoneal abscess	1 (2.27%)	4 (9.52%)	.197
Incision infection	2 (4.55%)	8 (19.04%)	.047
Total	3 in 2 patients	14 in 10 patients	

the levels of IL-2, IL-10, and nitric oxide (NO), which would destroy the intestinal mucosa and result in BT.¹⁷ Moreover, a series of cytokines related to SIRS, including CRP, TNF- α and IL-6, which are also called proinflammatory factors are blamed for the process of BT.¹⁸

About Bacterial Translocation

The superficial area of the human intestinal mucosa is approximately 300 m², which guarantees the organisms to take in enough nutrient substances. Meanwhile, many types of bacteria exist in the intestinal tract, weighing

approximately 1 to 2 kg among all of the intestinal contents. Along with the extension to the terminal of the ileum, the number of the bacteria increase. Once passing the Bauhin's valves, the density of bacteria could increase sharply from 10² to 10³/g to 10¹⁰ to 10¹²/g. Therefore, the intestinal tract is also a huge infection base for humans.¹⁹ When an organism suffers excessive stress reaction or disorder, the intestinal tract microorganisms, toxin parasitizing, and antigens would penetrate the barrier of the intestinal mucosa and invade the previous aseptic intestinal tissue, such as the placenta percreta of intestinal wall, the lymphoglandulae

Table 3. The Results of Logistic Single Regression Analysis.

Influence Factors ^a		Sample Size	Number of SIRS Mitigation (%)	χ^2	P
X1	0	44	38 (86.4)	10.408	.001
	I	42	23 (54.8)		
X2	0	62	45 (72.6)	0.293	.588
	I	24	16 (66.7)		
X3	0	52	40 (76.9)	2.291	.130
	I	34	21 (61.8)		
X4	0	50	35 (70.0)	0.050	.823
	I	36	26 (72.2)		
X5	0	79	59 (74.7)	—	.020
	I	7	2 (28.6)		
X6	0	78	59 (75.6)	—	0.007
	I	8	2 (25.0)		
X7	0	67	51 (76.1)	3.960	.047
	I	19	10 (52.6)		
X8	0	83	60 (72.3)	—	.201
	I	3	1 (33.3)		
X9	0	58	46 (79.3)	6.067	.014
	I	28	15 (53.6)		
X10	0	41	28 (68.3)	0.264	.607
	I	45	33 (73.3)		
X11	0	59	45 (76.3)	2.600	.107
	I	27	16 (59.3)		
X12	0	67	50 (74.6)	2.010	.156
	I	19	11 (57.9)		

Abbreviation: SIRS, system inflammatory response syndrome.

^aAggravated factors for SIRS (X): X1, pneumoperitoneum (yes ~ 0 / no ~ 1); X2, age (<50 years old ~ 0 / ≥50 years old ~ 1); X3, body mass index (<30 kg/m² ~ 0 / ≥30 kg/m² ~ 1); X4, course of disease (CD) (<48 h ~ 0 / 72 h > CD > 48 h ~ 1); X5, pathological type of appendicitis (non-gangrene ~ 0 / gangrene ~ 1); X6, infected by multidrug resistant bacteria or not (no ~ 0 / yes ~ 1); X7, duration of operation (DO) (<60 min ~ 0 / ≥60 min ~ 1); X8, anesthesia (general anesthesia ~ 0 / spinal anesthesia ~ 1); X9, length of incision (≤1 cm ~ 0 / >1 cm ~ 1); X10, number of incisions (≥1 ~ 0 / <1 ~ 1); X11, usage of specimen bags (no ~ 0 / yes ~ 1); X12, WHO pain grade on first postoperative day (≤II ~ 0 / > II ~ 1).

mesentericae, portal system, and other distant organs with a result of infection, called BT.²⁰

Polat et al²¹ have found in a rat model that BT started when the intra-abdominal pressure reached 14 mm Hg. More prominent BT was observed when the intra-abdominal pressure reached the 20 or 25 mm Hg levels. However, some scholars have found that the inflammation of the CO₂ pneumoperitoneum group is more severe than the laparotomy group, without a statistical difference for BT, which may be related to the operation and the pathologic factors of peritonitis.²²

A study found that *Bacillus coli* could translocate in the intestinal tract in children with AA. With the aggravation of appendicitis, the incidence rates of BT and SIRS were increasing. It has been reported that BT occurring in

AA children had intimate connection with NO, which could be the incipient damaging factor in the intestinal mucosal barrier.²³ By contrast, studies about adults with BT caused by AA are insufficient. The relation between CDP and BT remains undefined.

The Effects of CDP on SIRS

The era of minimally invasive surgery has come and the laparoscopy has become the main surgical method. There are some viewpoints, although they are controversial, about using the CDP to treat BP, SIRS, and the effects of BT on the abdominal cavity. Some studies have shown that CDP could obviously inhibit the function of proinflammatory factors, such as CRP, TNF- α , and IL-6, after the operation.²⁴ This suppressive effect could relieve the symptoms or even stop the chain reaction of SIRS. Some studies have revealed that CDP can adjust the immune response, reduce the possibility of bacterial contamination in the abdominal cavity, and abate the incidence rates of septicemia for rats with severe peritonitis after abdominal operation.²⁵ Furthermore, Hanly et al²⁶ found that CDP can increase the level of IL-10 and decrease the level of TNF- α , providing evidence that CDP can reduce the mortality of animal models with septicemia.

Some studies have found that CDP could result in an increase of pressure in the abdominal cavity. The extension and deformation of human peritoneal mesothelial cells (HPMCs) in the diaphragmatic surface and the increase in intercellular space can enhance the openings of celiac lymphatic vessels, which would allow bacteria to enter the blood circulation and cause BT in the liver, lung, spleen, kidney, lymphoglandulae mesentericae, and other organs.²⁷ However, other studies presenting different opinions noted that the incidence rate of BT under CDP was not significantly higher than that under laparotomy for the animal models with intra-abdominal infection.²⁸ Moreover, there was no significant difference in the incidence rate of bacteremia, endotoxemia, and clinical sepsis between CDP and laparotomy.^{29,30}

Findings of This study

The results of this study indicated that compared with the preoperative levels, the postoperative levels of WBC, CRP, TNF- α and IL-6 in blood were apparently decreased in the laparoscopy group. These inflammatory factors results were in accordance with de Oliveira Machado's team,³¹ indicating that WBC, CRP, TNF- α , and IL-6 can sensitively predict the prognosis for appendicitis. Furthermore, the levels of WBC, CRP, TNF- α , and IL-6 were almost normal on the fourth day after operation for patients in the laparoscopy group. However, the levels of

Table 4. The Results of Logistic Multiple Regression Analysis.

Independent Variables X ^a	Regression Coefficient	Standard Deviation	Wald Value	P	exp(β) OR Value
X1	2.192	0.636	11.872	.001	8.956
X5	1.017	0.474	4.801	.019	2.266
X6	1.382	0.550	6.314	.012	3.984
X7	0.893	0.506	3.115	.058	2.442
X9	1.538	0.892	2.974	.085	4.658

^aIndependent variables for system inflammatory response syndrome (SIRS) (X): X1, pneumoperitoneum (yes ~ 0 / no ~ 1); X5, pathological type of appendicitis (non-gangrene ~ 0 / gangrene ~ 1); X6, infected by multidrug resistant bacteria or not (no ~ 0 / yes ~ 1); X7, duration of operation (DO) (<60 min ~ 0 / ≥60 min ~ 1); X9, length of incision (≤1 cm ~ 0 / >1 cm ~ 1). Dependent variable (Y): Y, SIRS (mitigate ~ 0 / aggravate ~ 1).

WBC, CRP, TNF- α , and IL-6 in blood were still increasing on the first day after the operation, although they declined on the fourth day after operation for patients in the control group. The difference in the descending speed of inflammatory factors between the groups could be due to the postoperative stress responses, which are related to the surgical methods.³²

There was no difference in septicemia and peritoneal abscess between the groups, whereas the incidence rate of incisional wound infection in the laparoscopy group was apparently lower than that in the control group (4.55% vs 19.04%); this finding was different from the report of Aranda-Narváez et al,³³ with an incisional infection rate of 13% for laparoscopy group but 14% for the open laparotomy group. The reasons for the aforementioned difference were related to the following: Some of the patients on whom laparotomy was performed lived in villages and were far from hospitals; thus, they were delayed for surgery, which is in accordance with the conclusion of Kong et al,³⁴ who hold a view that rural origin is identified as an independent indicator of poor outcome. Besides, the usage of specimen bags could prevent incision from the resected appendix. The average incisional infection rate of the 86 AA patients in our study was 11.63%, which was similar to the result of Aranda-Narváez et al³³ of 13.5%, implying that both laparoscopy and laparotomy are safe for patients with BT resulting from AA. Above all, we could get a conclusion that the CDP will not increase the incidence rate of BT in patients with BP caused by AA.

Through ANOVA, it was found that age, body mass index, course of disease, anesthesia, number of incisions, usage of specimen bags, and the grade of WHO Pain Grade System (WPGS) on the first preoperative day were the less prevalent factors on influencing SIRS ($P = .588, .130, .823, .201, .607, .107$, and $.156$, respectively, Table 3). Non-pneumoperitoneum, gangrenous appendicitis, multiple drug-resistant infections, over 1-hour duration of operation, and over 1-cm incision length could be the potential influential factors on the aggravating SIRS ($P = .001, .020, .007, .047$, and $.014$,

respectively, Table 3). A binary logistic regression analysis among the 5 factors above showed that non-pneumoperitoneum, gangrenous appendicitis, and multidrug resistant infections were verified as the potential independent influencing factors for SIRS aggravation ($P = .001, .019$, and $.012$, respectively, Table 4). These binary logistic regression results were consistent with the results of Tsioplis et al,³⁵ who showed that pathological type, the ongoing peritonitis, and surgical methods were the risk factors for AA. However, the difference between our study and that of Tsioplis et al³⁶ mainly included the presence of multidrug resistant bacteria, which are resistant to most of the antibiotics used in surgical department, and these types of bacteria could shift from peritoneal cavity to the other organs, with the possibility of incisional infection.

Our data verified that CDP is safe for BP and could be a potential protective factor to mitigate BP effectively, which was in agreement with the study by Thomson et al,³⁷ indicating that it is feasible to control SIRS with the performance of laparoscopy operation under CDP; at the same time, CDP would not raise the incidence rate of BT. For future studies about AA patients undergoing CDP, more subjects and more information should be collected in studies with a larger sample size and a longer follow-up period.

Highlights

- Carbon dioxide pneumoperitoneum (CDP) could be potential protective factors to control SIRS effectively.
- CDP does not increase the probability of bacterial translocation.
- CDP is safe and beneficial for patients with bacterial peritonitis caused by acute appendicitis.

Author Contributions

Study concept and design: Huaidu Peng, Junshuo Zhang
Acquisition of data: Chudong Cai
Analysis and interpretation: Xi Fang
Study supervision: Junwei Wu

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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