Journal of Pediatric Surgery 60 (2025) 162409

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.sciencedirect.com/journal/journal-of-pediatric-surgery

Systemic and Peritoneal Effects of Pneumoperitoneum in Pediatric Laparoscopy

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ARTICLE INFO

Article history:
Received 7 February 2025
Received in revised form 30 April 2025
Accepted 5 June 2025

Keywords:
Laparoscopy
Pneumoperitoneum
Histological changes
Cytokine

ABSTRACT

Background: Laparoscopy is a standard procedure for both children and adults. However, the potential effects of CO_2 insufflation on the peritoneum remain unclear. This multicenter study aimed to assess the plasma levels of inflammatory markers and examine tissue changes in children who underwent pneumoperitoneum (PN) and laparoscopic surgery.
Methods: From 2021 to 2023, patients who were candidates for elective laparoscopic surgery were divided into two groups based on their duration of PN: ±1 h. Serum samples were collected preoperatively (T0) and 24 h postoperatively (T1). Tumor necrosis factor-α, interleukin (IL)-6, IL-8, and regulated on activation, normal T cell expressed and secreted cytokine levels were quantified. Additionally, samples of the peritoneal serosa were obtained for double-blind histological evaluation at the beginning (T0) and end of the procedure (T1). The results are expressed as means ± standard deviations, and significance was set at $P < 0.05$.
Results: The study included 47 children with a median age of 12 (group A, n = 30; B, n = 17). The chemokine values at T0 and T1 did not show significant variations in either group, except for IL-8, which significantly decreased from T0 to T1, especially in group B. A peritoneal histological study showed moderate focal hyperplasia of the mesothelium and the presence of a light inflammatory infiltrate in T1 versus T0. These peritoneal changes were more present in group B than in group A.
Conclusion: PN significantly reduced IL-8 levels and induced minor histological changes in the peritoneum, primarily in group B. Laparoscopic surgery minimally affected the integrity and biology of the peritoneum, resulting in beneficial effects on the immune system.

1. Introduction

Laparoscopy has become increasingly popular in many procedures, even in children, due to its numerous advantages over open abdominal surgery. In particular, laparoscopy offers better cosmetic results, shorter hospital stays, less postoperative pain, and a more rapid return to daily activities [1]. However, some comorbidities, including mild pain, abdominal discomfort, and development of adhesions, have been reported [2–4]. Using pneumoperitoneum (PN) is critical in laparoscopic surgery because it provides visibility and enables surgeons to handle all intra-abdominal contents. Nevertheless, it can alter abdominal homeostasis and induce metabolic changes through mechanical and biochemical effects [4–8]. The use of CO_2 can potentially cause metabolic, immunological, and structural changes in the peritoneum [9,10], impacting clinical outcomes, such as postoperative pain, length of hospital stay, and recovery time [11–16]. CO_2 can lead to inflammation or significant changes in the peritoneum, highlighting its impact on tissue health [17]. Moreover, the degree of morphological changes is linked to the level of intrabdominal pressure, and the insufflation of CO_2 evokes a response by modifying factors, such as plasma and

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https://doi.org/10.1016/j.jpedsurg.2025.162409

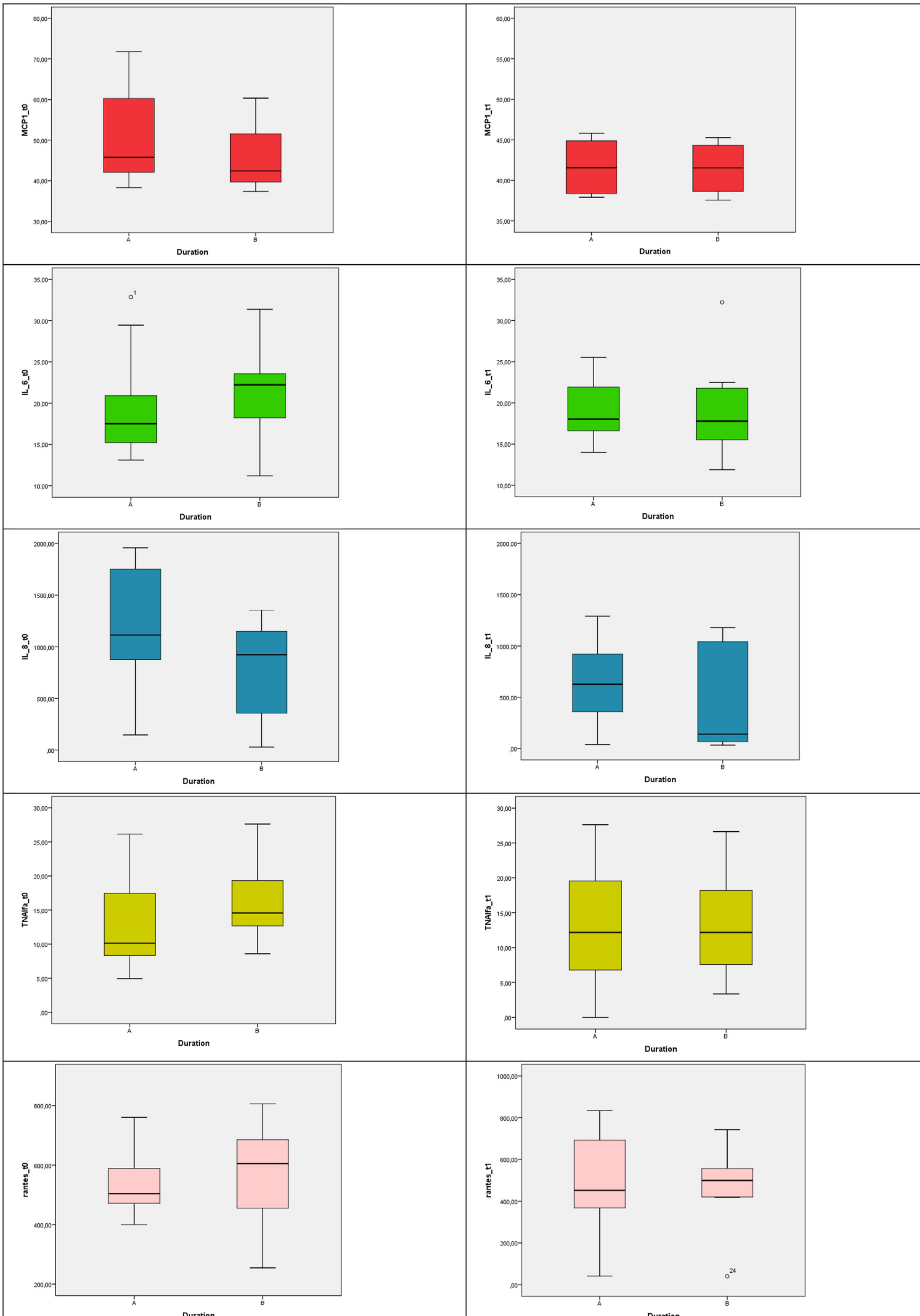

Fig. 1. Boxplot of cytokine distribution in groups A and B in two-time points.

Table 1
Descriptive statistics for variables in two time points. MCP-1, monocyte chemoattractant protein-1; IL, interleukin; TNF, tumor necrosis factor; RANTES, regulated on activation, normal T cell expressed and secreted.

Variables	T0	T1	P-value
MCP1	51.89 ± 19.58	44.25 ± 10.92	0.136
IL-6	20.67 ± 5.86	19.34 ± 4.71	0.654
IL-8	**1387.05 ± 1561.11**	**553.30 ± 452.82**	**0.045**
TNF-α	14.51 ± 6.48	12.77 ± 8.34	0.232
RANTES	549.58 ± 141.32	481.36 ± 206.86	0.390

Table 2
Descriptive statistics for variables in two groups and time points. MCP-1, monocyte chemoattractant protein-1; IL, interleukin; TNF, tumor necrosis factor; RANTES, regulated on activation, normal T cell expressed and secreted.

Variables	Group A		P-value
	T0	T1	
MCP1	55.01 ± 22.92	45.64 ± 13.26	0.208
IL-6	19.40 ± 6.12	19.31 ± 3.77	0.929
IL-8	1466.81 ± 1349.72	642.91 ± 399.86	0.263
TNF-α	12.92 ± 6.90	12.47 ± 9.154	0.859
RANTES	541.03 ± 107.95	483.60 ± 234.23	0.480
	Group B		**P-value**
Variables	**T0**	**T1**	
MCP1	45.64 ± 10.10	41.47 ± 3.48	0.465
IL-6	21.93 ± 5.53	19.36 ± 5.91	0.374
IL-8	**1291.33 ± 955.07**	**433.82 ± 528.49**	**0.043**
TNF-α	16.23 ± 5.78	13.15 ± 7.79	0.052
RANTES	558.13 ± 172.62	478.66 ± 181.03	0.646

peritoneal chemokine levels [18]. Previous studies have reported that laparoscopy induced a lower inflammatory response than laparotomy in children who underwent fundoplication by comparing the inflammatory reaction after open and laparoscopic fundoplication. The plasma levels of IL-10, anti-inflammatory cytokines, were significantly higher in the open group than in the laparoscopic group [19]. According to Jukic et al., the laparoscopic approach to inguinal hernia repair significantly reduces inflammatory surgical stress compared with the open approach [20].

Few studies have described the histological peritoneal changes during laparoscopic surgery in humans. Liu et al. examined peritoneal morphology using an electronic microscope in 40 patients with myoma of the uterus or simple ovarian cyst who underwent conventional or laparoscopic surgery. These findings showed that PN resulted in mesothelial cell protrusion, which was immediately apparent [21]. Intercellular spaces between mesothelial cells were observed at 30 min, the underlying basement membrane became visible and lost its continuity at 1 h, and by 2 h, chronic cellular infiltrates appeared in the intercellular spaces. In 20 biopsies taken from the working area after laparoscopic cholecystectomy, Tarhan et al. also observed mesothelial cell apoptosis and other ultrastructural changes in biopsies from the working area after laparoscopic cholecystectomy [22]. To our knowledge, this is the first study to examine the peritoneal histological changes in children who have undergone laparoscopy. Pneumoperitoneum is a critical component of laparoscopy; however, it has notable effects on physiological processes, particularly in pediatric populations when considering somatic development from newborns to adolescent. This phenomenon is intricate and exerts considerable influence on the subject homeostasis. Children differ from adults, so adult recommendations can't be directly applied to them [23]. Surgical outcomes have been studied separately but rarely compared in pediatric and adult populations, leaving a gap in understanding how pediatric surgical outcomes differ from those of adults. McMullin et al. found that children experience higher rates of surgical site infections (SSI) after laparoscopic appendectomy and laparoscopic cholecystectomy, increased readmission rates following laparoscopic appendectomy, and longer lengths of stay in

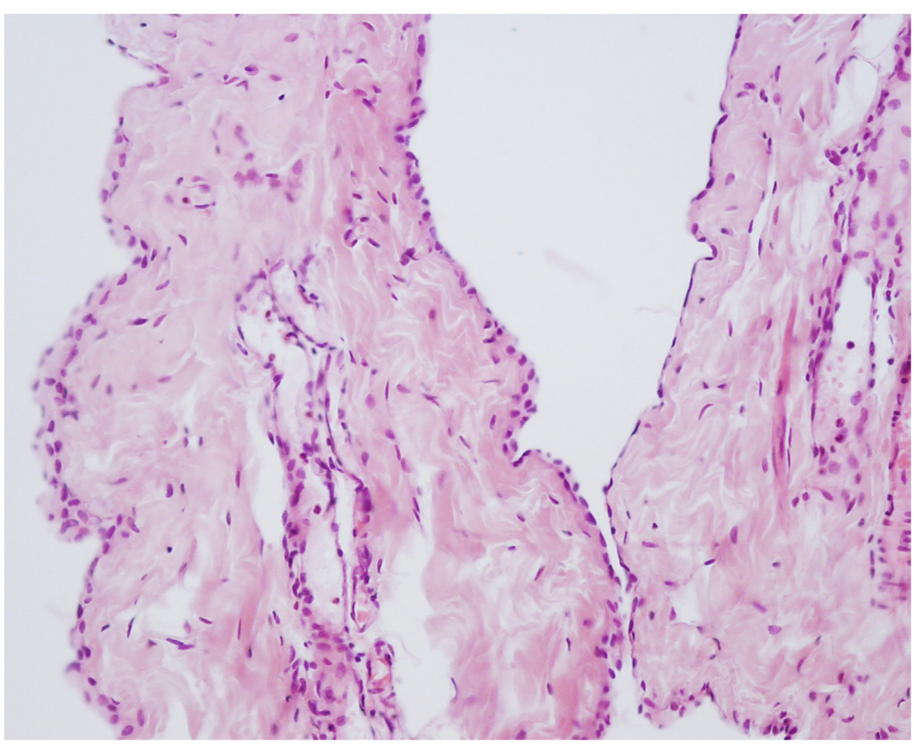

Fig. 2. Reactive mesothelium (left side Group B) vs. normal mesothelium (right side).

all cases [24]. Therefore, this study aimed to assess the inflammatory markers and histological tissue modifications in children undergoing PN and laparoscopic surgery.

2. Ethical approval

The study protocol has been approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli" (0007953 of 06/04/2020).

3. Materials and methods

This multicenter study, conducted across three Pediatric Surgery Units, involved pediatric patients aged 10 to 13 who were candidates for elective laparoscopic surgery from 2021 to 2023. The laparoscopic procedures performed included inguinal hernia repair, treatment of varicocele using the Palomo technique, and cholecystectomy. Patients with genetic syndromes, immune system alterations, or acute or chronic inflammatory diseases were excluded due to their potential influence on the data. For the PN, CO_2 was insufflated at 1.5 L/min, at body temperature, and 8–12 mmHg pressure in relation to the patient's age. The patients were divided into two groups based on the duration of PN as follows: group A, children with PN duration <1 h, and group B, children with PN duration >1 h. Serum samples (stored at −20 °C for analysis) were collected from the patients preoperatively (T0) and 24 h postoperatively (T1). The levels of specific cytokines (tumor necrosis factor alpha [TNF-α], interleukin (IL)-6, IL-8, monocyte chemoattractant protein-1 [MCP1], and regulated on activation, normal T cell expressed and secreted [RANTES]) were measured by enzyme-linked immunosorbent assay using MyBioSource (San Diego, CA, USA) kits, following the manufacturer's instructions. The intra- and inter-assay coefficients of variability (CV) were 5.45 % and 5.54 % for RANTES, respectively, and ≤6.3 % and ≤8.6 % for IL-8, respectively. All serum samples were appropriately diluted. For TNF-α and IL-6, the intra- and inter-assay CVs were ≤8 % and ≤12 %, respectively. All the optical densities were measured at 450 nm.

4. Histopathological examination

Samples of the peritoneal serosa were obtained for double-blinded histological and morphological evaluation at the beginning (T0) and end of the surgical procedure (T1). The T0 sample was obtained during the umbilical open approach according to the Hasson technique, without CO_2 insufflation.

All the specimens were fixed in 10 % neutral-buffered formalin, and paraffin was used for embedding. Subsequently, 4-μm-thick sections were cut and routinely stained with hematoxylin and

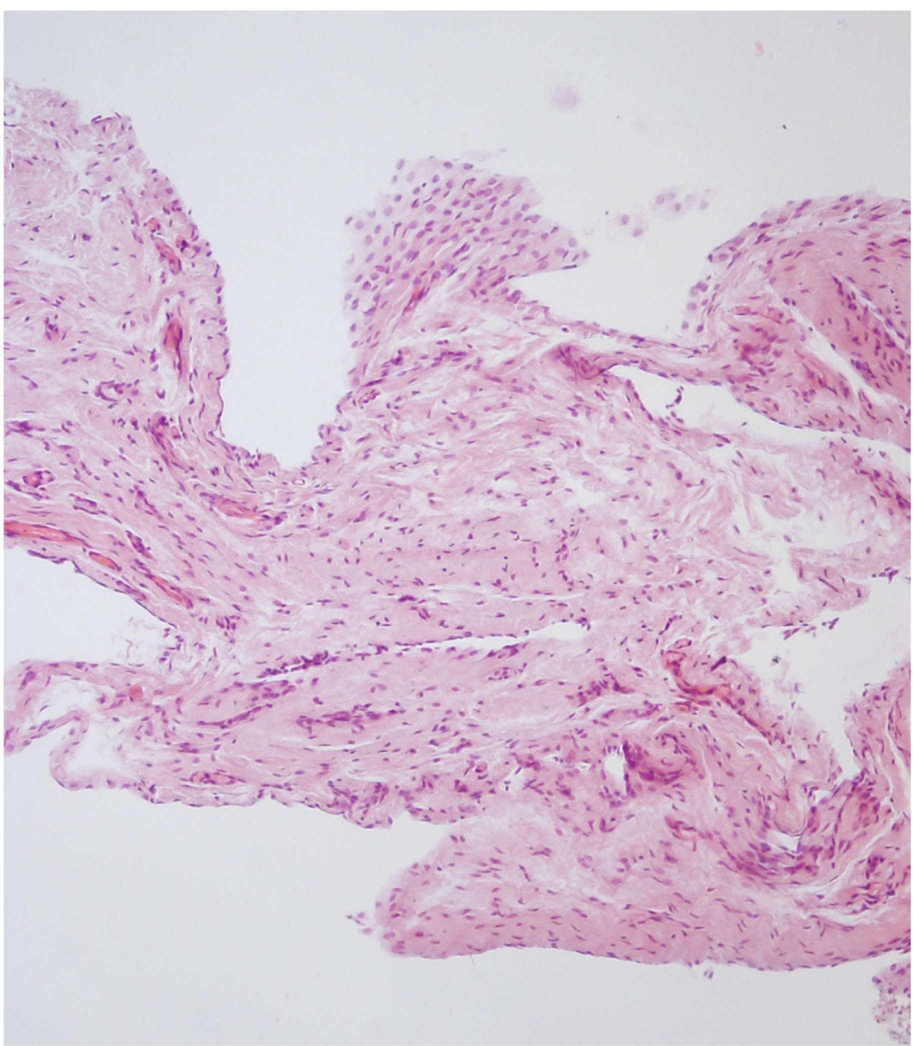

Fig. 3. Moderate focal mesothelial hyperplasia (Group a): low magnification.

eosin for histological evaluation. The samples were examined and photographed using a light microscope (Eclipse E600, Nikon, Melville, NY, USA) equipped with a microphotography system (Nikon Digital Camera DMX1200, Melville, NY, USA). The mesothelium, vessel congestion, and inflammatory infiltrates were evaluated in each sample.

5. Power and sample size calculation

The sample size was calculated considering IL-8 variation (preoperatively vs. 24 h postoperatively) as the primary outcome for patients undergoing laparoscopy as the primary outcome for patients undergoing laparoscopy, using the methodology outlined by Knatten et al. [19]. Assuming an effect size of 0.45 for the difference between two dependent means and a significance level of 5 %, the minimum number of participants to be enrolled to obtain a statistical power of 80 % was calculated as 41 using the G*power package version 3.1.9.4. Therefore, 47 participants were enrolled in this study.

6. Statistical analysis

Differences between treatments were evaluated using variance analysis to analyze each cytokine's effects. The results are expressed as means ± standard deviations, and $P < 0.05$ was considered significant.

Numerical data are expressed as medians and interquartile ranges (Q1–Q3), and categorical variables are described as absolute frequencies and percentages. A non-parametric approach was used because the numerical variables were non-normally distributed, as verified by the Kolmogorov–Smirnov test.

Table 3
Histological changes in study groups at T1.

Histological change	Group A, T1 % (n)	Group B, T1 % (n)
Vascular congestion	46,7 % (14)	52.9 % (9)
Inflammation	36.7 % (11)	64,7 % (11)
Mesothelial hyperplasia	6.7 % (2)	32.3 % (6)
Endothelial hyperplasia	–	11,8 % (2)

To compare two consecutive time points (T0 vs. T1), the McNemar test was applied for dichotomous variables (congestion and inflammatory infiltrate), and the Wilcoxon test was applied for numerical variables (MPC1, IL-6, TNF-α, IL-8, and RANTES).

The Spearman correlation test was used to assess the significant interdependence between PN duration and other variables such as vessel congestion at T1, delta IL8 (variation from T0 to T1), delta MPC1, delta IL6, delta TNF-α, delta IL-8, and delta RANTES.

All the statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, IBM Corp.).

Significance was set at $p < 0.05$.

7. Results

The study included 47 children: 30 in group A and 17 in group B, with a median age of 12 years (range, 10–13). The patients enrolled in the study were subjected to PN for a mean duration of 36 min in group A and 103 min in group B.

The mean pressure was 12 mmHg in both groups, with an average insufflation of 3.2 l/min. The amount of insufflated CO_2 was 23 l in group A and 80 l in group B. The patients in group A underwent repair for inguinal hernia in 5 cases, cholecystectomy in one case and treatment for varicocele in 24. In group B, the procedures were 8 cholecystectomies, 6 inguinal hernia repairs and 3 treatments for varicocele.

None of the chemokine values at T0 and T1 showed significant variations (Fig. 1). The mean values of RANTES, TNF-α, MCP1, and IL6 chemokines at T0 and T1 were 549.58 pg/mL vs. 481.36 pg/mL, 14.51 pg/mL vs. 12.77 pg/mL, 51.89 pg/mL vs. 44,25 pg/mL, and 20.67 pg/mL vs. 19.34 pg/mL, respectively (Table 1).

The IL-8 concentration significantly decreased from T0 to T1, with mean values of 1387.05 vs. 553.30 pg/mL ($P = 0.045$) (Table 1).

By analyzing the single group, no significant differences in chemokine values were observed between groups A and B (Table 2). In contrast, the mean values of IL-8 in group B were significantly reduced at T1 compared to that at T0 (1291.33 pg/mL vs. 433.82 pg/mL).

Histological examination of the peritoneum revealed moderate focal hyperplasia of the mesothelium (Fig. 2) and a mild inflammatory infiltrate (Fig. 3) that was more present in group B than in group A (Table 3).

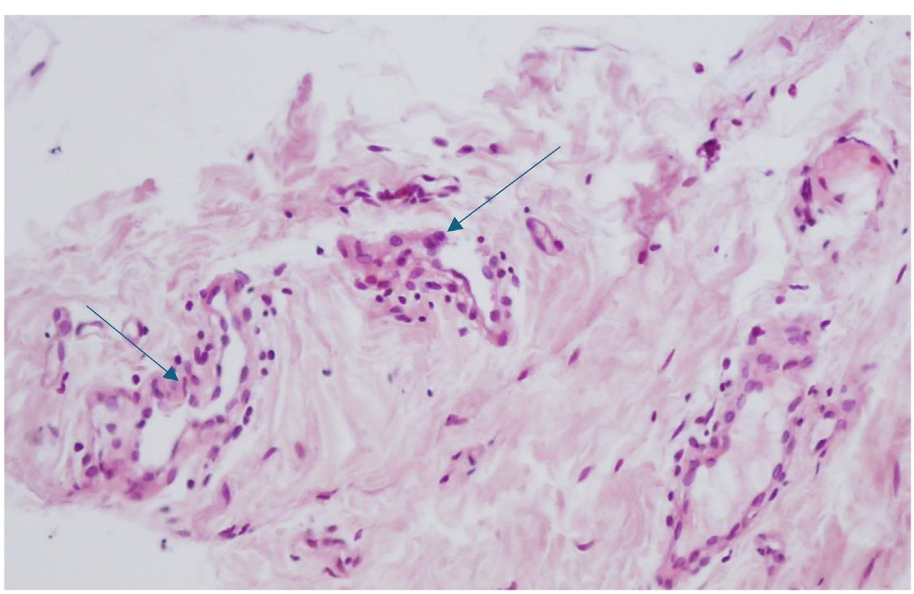

Fig. 4. Endothelial activation and some lymphocytes (Group B).

At T1, vascular congestion was almost similar in both groups (46.7 % and 52.9 %), while inflammation, characterized by rare lymphocytic cells, occurred more frequently in Group B (64.7 %) compared to Group A (36.7 %). Mesothelial hyperplasia was more common in Group B (32.3 %) than in Group A (6.7 %). Endothelial hyperplasia was present only in Group B (11.8 %) (Fig. 4). Double-blind histological evaluation revealed no changes at T0.

8. Discussion

CO_2 insufflation is essential in minimally invasive laparoscopic surgery. Therefore, understanding its effects on the peritoneal environment is crucial to optimize surgical outcomes and patient safety. We are faced with the puzzle where controlling every variable within the laparoscopic technique, not just the surgical procedure, is critical. CO_2 modifies the peritoneum and causes an imbalance in its functions, including peritoneal acidosis, the release of proinflammatory cytokines, and changes in the immune response. However, laparoscopy induces a less severe peritoneal reaction than open surgery [22,23]. Nevertheless, our study revealed that the chemokine assay results did not change from baseline, suggesting that the laparoscopic technique causes minimal surgical stress. The IL-8 dosage significantly decreased compared to baseline values, as shown in other studies. Bohne et al. examined the effects of laparoscopic versus open surgery on the immune response in patients with colorectal cancer. They reported that IL-8 levels might decrease after laparoscopic surgery compared to those following open surgery [23]. The proinflammatory domain of this interleukin results in better outcomes at lower concentrations and improved oncological outcomes. Kratten al. investigated the inflammatory response after open and laparoscopic fundoplication in children [19]. In their study, the open surgery group had significantly higher plasma levels of IL-10 than the laparoscopic surgery group. However, the levels of proinflammatory cytokines (TNF-, IL-6, IL-8, and MCP-1), white blood cell counts, and C-reactive protein levels were not significantly different between the two groups. According to the authors, laparoscopic surgery did not significantly reduce inflammatory response compared to open surgery in children undergoing fundoplication. Jukic et al. [20] have suggested that the laparoscopic approach is more effective than the open approach for the surgical repair of inguinal hernias. This effectiveness is attributed to a significant reduction in inflammatory surgical stress associated with laparoscopic surgery. The differences in outcomes can be explained by the variations in surgical procedures and the type of anesthesia used. The experimental model demonstrated that adjusting PN parameters during laparoscopy can mitigate the early effects associated with CO_2 insufflation. Studies in rats have reported a connection between peritoneal insufflation with CO_2 and infiltration of eosinophils, mast cells, and macrophages. Cellular and systemic responses were also observed after 24 h [17,18]. In addition to the lack of chemokine changes, we observed no significant histological changes in the peritoneum after laparoscopy. This finding supports the use of minimally invasive surgery owing to gentle tissue handling, the use of microsurgical instruments, and a smaller operative field. Nevertheless, a theoretical concern is that pneumoperitoneum and elevated intra-abdominal pressure could cause bacteremia and a systemic response during laparoscopic surgery for acute and chronic inflammatory diseases. Data on pneumoperitoneum's impact on physiological changes and systemic inflammation during sepsis are limited and controversial [25]. In contrast, laparoscopic surgery showed a reduced risk of septic shock or sepsis among ulcerative colitis patients who had previously used chronic steroids before the procedure. This indicates that minimally invasive surgery may be a beneficial choice for this particular group of patients [26].

In our study, morphological findings revealed mild modifications such as congestion, hemorrhage, tissue infiltration of inflammatory cells, and focal hyperplasia of the peritoneum, primarily in patients with PN, which lasted for >1 h. Few studies have investigated adult mesothelial damage after PN. To the best of our knowledge, this is the first study to examine peritoneal histological changes in children who underwent laparoscopy. However, the results may have been influenced by differences in age, immunological response characteristics, and a limited number of cases. Tarhan et al. observed mesothelial cell apoptosis, cellular bulging, intercellular clefts, and ultrastructural alterations in 20 biopsy specimens from the working area after laparoscopic cholecystectomy [22]. Liu et al. have reported that CO_2 PN during laparoscopic surgery can lead to significant changes in the peritoneum, with insufflation duration being a factor [27]. These data contradict our histopathological findings, which show fewer significant modifications after PN. Controlling all parameters influencing PN, such as temperature, pressure, flow rate, and humidity, may be essential for inducing mesothelial damage. In an experimental study, our group highlighted the correlation between the grade of morphological peritoneal changes and the level of intrabdominal pressure [28]. Low CO_2 pressure has a negligible effect on peritoneal changes compared to high pressure and air inhalation [28,29]. Moreover, experimental evidence suggests that the development of adhesion can be influenced by insufflation pressure. Matsuzaki et al. investigated the effects of intraperitoneal pressure on PN in humans and animals [30]. They affirmed that a low intra-abdominal pressure and short laparoscopic surgery can mitigate the impact on the peritoneal surface and the effects of fibrinolytic activity. Kielen et al. suggested that laparoscopic abdominal surgery reduces the incidence of adhesion-related readmission [31]. Nevertheless, this study included a broad spectrum with highly varying potential for adhesion formation. In our study, we lack long term follow-up and clinical data to verify the impact of adhesion development in a pediatric cohort and a small sample size may make it difficult to determine whether a particular outcome is a true finding.

Therefore, even if the sample size was determined to be sufficient for chemokine data, based on 47 patients, the absence of long-term follow-up could present a limitation for the study.

Understanding how laparoscopy and PN affect fundamental physiological mechanisms is essential for enhancing minimally invasive surgeries further effective. The peritoneum, which lines the abdominal cavity, plays a key role in these changes that occur after laparoscopic procedures. A perfect balance between components and factors including chemokines and cytokines is essential for the activation and recruitment of leukocytes to inflammatory sites. Laparoscopic surgery affects the integrity, biology, and microcirculation of the peritoneum, positively influencing the immune system. Although the exact relationship between these factors and their clinical implications is unclear, understanding these mechanisms is crucial to advance minimally invasive surgeries.

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