

## Intestinal Fatty Acid-Binding Protein as a Biomarker of Gastrointestinal Ischemia in Laparoscopic Surgery

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### ABSTRACT

Laparoscopy is a widely used surgical technique noted for its safety, cost-effectiveness, and rapid recovery compared to laparotomy. However, it carries risks, particularly gastrointestinal complications, including gastrointestinal ischemia, which can arise from elevated intra-abdominal pressure (IAP) during procedures. This review discusses the role of intestinal fatty acid-binding protein (I-FABP) as a potential biomarker for detecting gastrointestinal ischemia in laparoscopic surgery. I-FABP, released from enterocytes upon injury, is a promising indicator of intestinal distress and has been linked to various gastrointestinal conditions. Elevated IAP during laparoscopy, essential for surgical visibility, can compromise organ perfusion and lead to ischemia, necessitating careful management. Monitoring I-FABP levels in high-risk patients could facilitate early detection and intervention, improving outcomes. This review underscores the need for further research to establish I-FABP's clinical utility and to determine optimal monitoring protocols, aiming to enhance patient safety and reduce postoperative complications associated with gastrointestinal ischemia.

**Keywords:** *Laparoscopy, Pneumoperitoneum, Intestinal Fatty Acid-Binding Protein.*

### 1. INTRODUCTION

Minimally invasive laparoscopy is essential for the diagnosis and treatment of various medical conditions. Laparoscopy is one of the most prevalent surgical procedures globally. Laparoscopy is favored for numerous surgical interventions because of its minimal surgical risks and complications. Laparoscopy results in reduced patient morbidity, abbreviated hospital stays, diminished complications, and enhanced cosmetic outcomes [1].

Laparoscopic procedures may result in complications. Laparoscopic procedures necessitate a pneumoperitoneum using CO<sub>2</sub> gas to enhance the surgeon's visibility [2]. Prolonged pneumoperitoneum may result in complications. Umano et al. examine extended CO<sub>2</sub> insufflation, which elevates intra-abdominal pressure and induces gastrointestinal stress and ischemia [3]. A separate study indicated that extended pneumoperitoneum diminishes microvascular perfusion and induces liver parenchymal damage [4].

Intestinal fatty acid-binding protein (I-FABP), a blood biomarker indicative of gastrointestinal ischemia initially identified in mice, has been discovered to exhibit analogous properties in humans [5]. A meta-analysis indicated that I-FABP serves as a diagnostic instrument for confirming gastrointestinal ischemia [6]. The current review article will examine I-FABP in the context of laparoscopic surgery.

#### *Laparoscopy*

##### **Intra-abdominal pressure**

Elevated intra-abdominal pressure (IAP) is a significant consideration in laparoscopy, extensively researched for its possible impact on many physiological systems and its correlation with adverse outcomes, particularly with gastrointestinal stress. The impact of elevated intra-abdominal pressure during laparoscopy has been a subject of investigation for numerous years. Research has especially investigated its impact on colonic anastomosis, intestinal perfusion, lactic acidosis, hepatic and renal

blood flow, intracranial pressure, and hemodynamic parameters.

The elevation of IAP during laparoscopy mostly results from the insufflation of carbon dioxide or alternative gases into the peritoneal cavity to provide an optimal visual field [7]. The introduction of gas elevates IAP, which is crucial for ensuring optimal visibility and effective manipulation during laparoscopic surgery [8]. Nonetheless, elevated intra-abdominal pressure IAP has been linked to numerous disadvantages, particularly with gastrointestinal distress. Research has predominantly concentrated on the adverse effects of elevated intra-abdominal pressure during laparoscopy, particularly those associated with gastrointestinal pain. Research indicates that extended pneumoperitoneum at elevated pressures may lead to lactic acidosis, diminished hepatic and renal perfusion, and disrupted respiratory and hemodynamic processes [7].

Moreover, elevated IAP has been linked to adverse impacts on stomach blood flow, standard hemodynamic metrics [9], and indicators of oxidative stress in the ovary [8]. Moreover, researchers have examined the impact of elevated intra-abdominal pressure on gastrointestinal motility, stress indicators, and pain responses. These studies have demonstrated that elevated IAP can induce stress responses and associated complications, including cardiovascular and cerebrovascular incidents, along with dysfunction in the gastrointestinal and neuroendocrine systems [10], [11], [12]. Moreover, elevated IAP correlates with alterations in respiration, hemodynamics, and immune responses, leading to heightened mucosal interleukin-6 (IL-6) concentrations and possible implications for peritoneal integrity and stress-induced immune reactions [13].

Elevated intra-abdominal pressure during laparoscopy has been linked to several physiological effects, including alterations in cardiac output, pulmonary artery pressure, hepatic blood flow, and propofol levels [14]. Furthermore, researchers have investigated elevated intra-abdominal pressure concerning its impact on intrauterine pressure, fetal respiratory acidosis, and hypoxia.

### **Carbon-dioxide insufflation**

The administration of CO<sub>2</sub> gas is a method employed in laparoscopic procedures to establish a clear visual field and sufficient space for maneuverability during the operation. CO<sub>2</sub> insufflation is an optimal technique for establishing pneumoperitoneum in laparoscopic surgery, owing to its safety, cost-efficiency, and practicality [2].

Nonetheless, CO<sub>2</sub> insufflation poses risks, including the potential for CO<sub>2</sub> embolism. This complication may occur during or immediately following the introduction of carbon dioxide into the human body cavity. CO<sub>2</sub> insufflation during laparoscopic surgery can elevate intra-abdominal pressure, adversely impacting liver function and cell-mediated immune responses. Moreover, the application of CO<sub>2</sub> insufflation in extraperitoneal laparoscopic procedures has been linked to the development of subcutaneous emphysema, pneumomediastinum, pharyngeal emphysema, and pneumothorax [3].

The potential oncological implications of CO<sub>2</sub> infiltration into the abdominal cavity during laparoscopic cancer surgery remain a topic of debate. Long-term laparoscopic procedures utilizing continuous cold and dry CO<sub>2</sub> have been identified as a potential contributor to hypothermia [15].

Additionally, in addition to the hazards linked to CO<sub>2</sub> insufflation, there are apprehensions regarding the potential presence of CO in the peritoneal cavity during laparoscopic surgery employing powered dissection [16]. Carbon monoxide poisoning remains prevalent and can lead to cardiac complications, delayed myocardial injury, and various cardiac disorders [17]. Emergency physicians must recognize the clinical manifestations of carbon monoxide poisoning, as fatalities frequently result from CO inhalation [18]. Furthermore, carbon monoxide poisoning may result in myocardial ischemia and cardiac conduction disorders [19]. Inhaling substantial quantities of carbon monoxide is detrimental to health and can result in significant health repercussions.

### **Pneumoperitoneum duration**

IAP is a critical parameter in laparoscopic surgery, with normal ranges typically between 5 to 7 mm Hg, but can rise to 14 mm Hg in obese patients. Intra-abdominal hypertension is defined as an IAP exceeding 12 mm Hg, while abdominal compartment syndrome occurs when pressures exceed 20 mm Hg [20], [21].

Laparoscopic surgery has been shown to significantly influence hemodynamic parameters, particularly through the effects of pneumoperitoneum, which is the insufflation of gas into the peritoneal cavity. The insufflation pressure, typically maintained between 12 to 15 mmHg, is crucial as it balances surgical visibility and access against the risk of hemodynamic instability and compromised organ perfusion. Studies indicate that increased intra-abdominal pressure can lead to a reduction in splanchnic blood flow, which is directly proportional to the level of pressure applied [22]. For instance, pressures as low as 10 mmHg have been associated with notable decreases in splanchnic perfusion, highlighting the delicate balance required during laparoscopic procedures [23].

Furthermore, the positioning of patients during laparoscopic surgery, such as the head-up or head-down positions, can exacerbate these hemodynamic changes. Research has demonstrated that extreme positions can further compromise splanchnic perfusion, particularly when combined with pneumoperitoneum [24]. The physiological alterations induced by these positions, along with the effects of pneumoperitoneum, can lead to significant hemodynamic shifts, necessitating careful monitoring and management during surgical procedures [25].

Laparoscopic surgery has gained prominence due to its minimally invasive nature, which is generally well tolerated in healthy patients. However, complications such as postoperative mesenteric ischemia are more frequently reported in individuals with significant cardiovascular comorbidities. This association highlights the importance of understanding the physiological impacts of laparoscopic techniques, particularly the effects of pneumoperitoneum, which can exacerbate cardiovascular instability in vulnerable populations [26].

The 'dial-down' technique is one strategy employed to mitigate the adverse effects of pneumoperitoneum. This method involves starting with standard inflation pressures and progressively reducing them to the minimum permissible level, thereby minimizing intra-abdominal pressure (IAP) and its associated cardiovascular effects [27]. Additionally, during laparoscopic procedures, it is advisable to avoid the reverse Trendelenburg position when feasible, as this position can diminish venous return and jeopardize cardiovascular stability, particularly in patients with pre-existing cardiovascular conditions [26]. Research indicates that the establishment of pneumoperitoneum can lead to various physiological changes, including increased IAP, which has been linked to reduced mesenteric venous flow and subsequent ischemia [28].

Furthermore, studies have shown that maintaining high flow rates during carbon dioxide insufflation can lead to unexpected cardiovascular changes, such as hypotension and bradyarrhythmia, especially in patients classified as ASA I and II [27]. Therefore, careful management of pneumoperitoneum and patient positioning is critical to ensure cardiovascular stability during laparoscopic surgeries, particularly in patients with significant comorbidities [26].

### **Intestinal fatty acid-binding protein**

Fatty acid binding proteins (FABPs), low molecular weight intracellular proteins (approximately 15 kDa), are essential for the transport and metabolism of long-chain fatty acids in the cytoplasm of cells that utilize fatty acids as an energy source [29]. Three isoforms of FABP are expressed in the intestine: intestinal fatty acid-binding protein (I-FABP), ileal bile acid-binding protein (I-BABP), and liver fatty acid-binding protein (L-FABP) [30]. I-FABP is exclusively present in mature enterocytes of the small intestine and colon, while L-FABP is located in the small intestine, colon, liver, and kidney [31].

Various forms of FABP, particularly I-FABP, are present in the epithelial cells of the small intestine mucosa. I-FABP immunoreactivity can be detected in the duodenum to the distal ileum through immunochemical staining using specific anti-I-FABP antibodies. I-FABP is readily released into plasma and excreted in urine, rendering it a valuable marker for enterocyte damage in both mediums [31]. I-FABP levels in healthy individuals should not surpass 2.0 ng/mL, and may even be undetectable [32].

A correlation exists between gastrointestinal disease and serum I-FABP concentration. Individuals with Crohn's disease exhibit a notable elevation in I-FABP [33]. Additional research on patients with small bowel obstruction demonstrated a notable elevation in I-FABP [34]. Abdominal trauma may elevate I-FABP levels [35]. The investigation lasted 30 minutes in the intestine under ischemic conditions, succeeded by a reperfusion phase [30]. Additional researchers have determined that serum I-FABP levels are elevated in individuals with COVID-19, ulcerative colitis, necrotizing enterocolitis, abdominal infections, abdominal surgery, and gastrointestinal ischemia [36], [37]. The results suggest that I-FABP may serve as a biochemical marker for diagnosing small bowel disease.

Prior research has identified I-FABP as a biomarker for gastrointestinal injury associated with cardiopulmonary bypass, coronary artery bypass, and surgeries involving the heart, aorta, and ENT (ear, nose, and throat) [38], [39], [40], [41], [42], [43]. Despite I-FABP being a significant marker of intestinal tissue damage, there is limited literature on plasma I-FABP levels following major abdominal surgery or laparoscopic procedures [37].

Research conducted by Camkiran et al. involving 35 patients undergoing cardiopulmonary bypass surgery and 16 patients undergoing coronary artery bypass surgery demonstrated a significant increase in I-FABP levels of 14.6% and 36.4%, respectively [43]. These levels gradually decreased at 12 hours postoperatively and fell below preoperative levels by 24 hours postoperatively. Cardiopulmonary bypass surgery, though infrequent, may lead to gastrointestinal complications characterized by ischemia and a significant mortality rate. Research conducted by Holmes et al., which involved 29 patients undergoing cardiopulmonary bypass surgery [38]. Three individuals experienced complications including diarrhea, gastrointestinal hemorrhage, and acute renal failure. All three exhibited I-FABP levels that decreased at 1 hour and 12 hours postoperatively, although these levels normalized at 24 hours postoperatively.

Aortic Cross Clamping (ACC) in abdominal aortic aneurysm surgery and Extra-Corporeal Circulation (ECC) in thoracic aortic aneurysm surgery can diminish blood flow to the gastrointestinal tract, resulting in ischemia. A study by Vermeulen Windsant et al. demonstrated an elevation in I-FABP levels before and after ACC and ECC [42]. In patients devoid of postoperative complications, I-FABP levels rose 15 minutes and 2 hours following ACC and ECC. Consistent with other studies, I-FABP levels returned to baseline within 24 hours postoperatively. In patients experiencing complications from postoperative gastrointestinal necrosis, there was an increase of up to 1,000% compared to those without complications, with a return to normal levels occurring 48 hours postoperatively. This phenomenon is also observed in research concerning cardiac surgery [39], [40].

The study by Bingold et al. assessed I-FABP levels in patients undergoing major abdominal surgery, categorizing them into two diagnostic groups: those with gastrointestinal cancer and those without [37]. Prior to surgery, patients with gastrointestinal cancer exhibited elevated I-FABP levels compared to those without gastrointestinal cancer. Post-surgery, I-FABP levels in patients with gastrointestinal cancer exhibited a tendency to decrease, whereas in patients without gastrointestinal cancer, they significantly increased. Conversely, I-FABP levels exhibited no significant difference before and after microscopic otorhinolaryngology surgery [41].

## 2. DISCUSSION

The growing utilization of laparoscopic methods in surgery highlights the necessity to tackle the related complications, especially those impacting the gastrointestinal (GI) system. Gastrointestinal ischemia is a significant factor in postoperative morbidity, particularly due to the increased IAP frequently associated with laparoscopic procedures. In this context, I-FABP appears as a potential biomarker for the early identification and management of gastrointestinal ischemia. This discourse will examine the ramifications of I-FABP in laparoscopic surgery, the physiological difficulties presented by increased IAP, and the prospects for incorporating I-FABP monitoring into clinical practice.

I-FABP is an intracellular protein predominantly located in the enterocytes of the small intestine. It is essential for the absorption and transportation of fatty acids, which are critical for cellular metabolism and energy generation. Increased serum concentrations of I-FABP indicate enterocyte injury, rendering it a significant biomarker for conditions such as intestinal ischemia, inflammatory bowel disease, and trauma [33]. I-FABP levels can markedly elevate in reaction to ischemic events, offering clinicians a dependable instrument for diagnosing gastrointestinal distress.

Elevated I-FABP levels have been correlated with gastrointestinal ischemia in multiple clinical scenarios, including cardiopulmonary bypass surgeries and abdominal trauma [35], [38]. The findings indicate that I-FABP may be employed to evaluate the integrity of the intestinal mucosa during surgical interventions. Moreover, the capacity of I-FABP to be easily identified in blood and urine renders it a compelling choice for non-invasive monitoring.

Laparoscopy, while beneficial due to its minimally invasive characteristics, necessitates the insufflation of gases, usually carbon dioxide, to establish a working space within the abdomen. This procedure enhances IAP, which is essential for preserving an optimal surgical environment. Prolonged or excessive IAP can impair blood flow to splanchnic organs, leading to ischemia and possible postoperative complications [7]. The physiological consequences of increased IAP are extensively documented, demonstrating detrimental effects on colonic anastomosis, intestinal perfusion, and overall organ function [10], [11].

Research demonstrates a direct correlation between IAP levels and the extent of organ perfusion compromise. Increased IAP has been linked to heightened lactic acidosis, reduced hepatic and renal perfusion, and changes in hemodynamic metrics [14]. These modifications highlight the necessity of meticulous oversight during laparoscopic procedures, especially in individuals with pre-existing conditions that may render them susceptible to ischemic incidents.

The incorporation of I-FABP as a biomarker in laparoscopic surgery may yield substantial clinical consequences. For high-risk patients, including those with cardiovascular comorbidities or advanced age, real-time monitoring of I-FABP levels could enable earlier detection of gastrointestinal ischemia. Increased I-FABP levels during surgery may necessitate prompt interventions, including alterations to the intra-abdominal pressure, optimization of fluid resuscitation, or adjustments to surgical techniques to restore sufficient blood flow to the compromised regions.

Furthermore, the implementation of I-FABP monitoring may aid in the establishment of standardized protocols designed to reduce the likelihood of gastrointestinal complications. The application of strategies to mitigate insufflation pressures or the use of deep neuromuscular blockade to decrease intra-abdominal pressure may be informed by I-FABP measurements. By establishing a definitive correlation between I-FABP levels and surgical procedures, clinicians could enhance their patient management strategies.

Although current literature endorses the potential of I-FABP as a biomarker for gastrointestinal ischemia, additional research is required to confirm its applicability in laparoscopic surgery. Future studies should focus on determining baseline I-FABP



levels in varied patient populations and evaluating the fluctuations of these levels during different laparoscopic procedures. Furthermore, research ought to concentrate on identifying precise I-FABP thresholds that correlate with ischemic occurrences, facilitating a standardized monitoring methodology.

Examining the timing of I-FABP elevation concerning surgical stressors will be essential. Determining the peak levels of I-FABP—whether immediately after insufflation, during particular surgical maneuvers, or postoperatively—may yield valuable insights for optimal monitoring strategies and intervention timing.

Ultimately, research investigating the correlation between I-FABP levels and patient outcomes in laparoscopic surgery could reinforce its significance in clinical practice. By analyzing postoperative complications alongside pre- and intraoperative I-FABP measurements, researchers can enhance their comprehension of the role of I-FABP in mitigating adverse events associated with gastrointestinal ischemia.

### 3. CONCLUSION

I-FABP holds significant promise as a biomarker for gastrointestinal ischemia during laparoscopic surgery. Its ability to reflect intestinal damage in real-time could enhance clinical decision-making, particularly in high-risk surgical populations. By integrating I-FABP monitoring into routine laparoscopic procedures, clinicians may be better equipped to anticipate and mitigate the risks of gastrointestinal ischemia, ultimately improving patient outcomes. Future research will be pivotal in establishing the validity and practicality of I-FABP as a standard monitoring tool in laparoscopic surgical practice, paving the way for more proactive and personalized patient care.

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