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Acute Pancreatitis Following Hepatic Resection: Pathogenesis and Emerging Treatments

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Abstract: ***Acute pancreatitis (AP) is a rare yet severe complication of liver resection, associated with high mortality rates. This review examines the incidence, pathogenesis, and treatment strategies for AP. Key factors include infections, biliary system dysfunctions, oxidative stress, and metabolic disorders. Effective management involves early interventions, including fluid resuscitation, nutritional support, and minimally invasive surgeries for severe cases. Future research should focus on precise diagnostic tools and targeted therapies to reduce complications and improve patient outcomes.***

Keywords: hepatectomy, acute pancreatitis, treatment, pathogenesis, postoperative complications

1. Introduction

In 1887, the German surgeon Langenbuch made a significant mark in the history of medicine by performing the first left lateral lobectomy in the history of mankind [1]. This pioneering surgical technique not only broke the limitations of liver surgery at that time, but also sowed the seeds of hope for the development of modern liver surgery. As the wheel of medicine rolls forward, hepatectomy has been continuously improved in the current of the times. From its humble beginnings as a single procedure, it has gradually evolved into a powerful weapon against a wide range of liver diseases, including choledocholithiasis and echinococcosis [2-4]. This surgical procedure has demonstrated compelling advantages in enhancing patient survival and improving postoperative quality of life. Contemporary medical technology is changing rapidly, and refinements in minimally invasive surgery, optimized anesthesia protocols, and innovative post-operative rehabilitation concepts all demonstrate the tireless spirit of discovery of medical practitioners. These breakthroughs are complemented by improved perioperative management, which greatly enhances surgical safety and keeps complication and mortality rates low [5]. Although modern medicine has made great strides in the field of liver surgery, postoperative complications remain an insurmountable chasm. Complications such as fever, hemorrhage, bile leakage, etc. follow the patient, and sequelae such as liver failure, pleural effusion, and subdiaphragmatic infection make the road to recovery full of thorns, and these challenges always test the wisdom and patience of medical practitioners [6-8].

As a special case of post-liver resection complications, acute pancreatitis (AP) is uncommon but often unexpected. The shockwaves of this complication are shockingly wide-ranging, from severe abdominal pain to multiorgan dysfunction, and are devastating. In the worst cases, the spell of pancreatic tissue necrosis accompanied by persistent organ failure is even more chilling, directly threatening the patient's precious life [9]. Given its potentially fatal nature, it is urgent to analyze the pathogenesis of this complication and explore efficient treatment options. Such systematic research not only improves patients' survival rate, but also promotes postoperative rehabilitation and improves the management system. It is worth mentioning that the results of this in-depth research not only provide a reliable basis for current clinical practice, but also a clear blueprint for the long-term development of the field of liver surgery, which is an important cornerstone for medical progress.

2. Incidence and influencing factors

The liver and pancreas, as vital digestive organs in the human body, play a crucial role in maintaining metabolic balance through their mutual coordination [10]. Studies have shown that dysfunction in either organ may lead to impairment in the function of the other, creating a pathway of mutual influence. AP after liver resection, a relatively rare but poorly prognostic postoperative complication, has garnered increasing attention in the clinical medical community. However, relevant literature and case reports remain relatively scarce, leaving clinicians lacking sufficient theoretical support and practical experience in diagnosis and treatment [11].

According to existing research data, the incidence of AP following liver resection is approximately 1.7% [9]. Although this figure may seem low, the mortality rate is as high as 20% to 40%, highlighting the severity of this complication [9, 12, 13]. Factors influencing the occurrence of postoperative AP include surgical procedures, patients' underlying diseases, and their overall health status. For instance, studies have shown that patients with chronic liver disease have a significantly higher probability of developing AP after liver resection compared to those without underlying liver disease [14]. Additionally, age is a non-negligible factor; elderly patients, due to decreased immune function and adaptability after surgery, are more prone to AP [15]. Furthermore, gender

differences also influence the incidence of AP to some extent, with data indicating that female patients have a higher likelihood of experiencing it after liver resection [16].

Patients with biliary diseases who undergo liver resection are also at high risk of developing AP [17]. The physiological changes brought about by surgery may make the pancreas more susceptible to impact. Moreover, extensive lymph node dissection and long-term ischemia caused by the Pringle maneuver are considered potential triggers for AP after liver resection [18]. The physiological trauma and stress response during surgery may further lead to pancreatic dysfunction. Of particular concern is that patients with hepatitis B who undergo orthotopic liver transplantation (OLTx) have a significantly increased incidence of pancreatitis, with studies showing that about 3% of such patients develop clinical pancreatitis, posing new challenges for clinical treatment [19]. Therefore, in-depth research on the pathogenesis and influencing factors of AP after liver resection holds significant clinical importance in reducing the incidence of this complication and improving patient survival rates.

3. Pathogenesis

3.1 Infection and inflammatory response mechanisms

3.1.1. Infection Triggers Inflammatory Response

The pancreas, as a highly active organ, may experience abnormal pancreatic juice secretion if infection occurs after liver resection. Infection is a rare but recognized cause of AP, with a variety of pathogens including mumps, measles or herpes viruses, Legionella, Leptospira or Mycoplasma bacteria, as well as some fungi or parasites. After liver resection, patients' immune systems are weakened, making them more susceptible to infections from surgical wounds or residual pathogens in the body [20]. Once infection occurs, it activates the body's inflammatory response system, releasing a large amount of inflammatory mediators such as interleukins IL-6, IL-8, and tumor necrosis factor TNF-α[21, 22]. These inflammatory mediators act on the pancreatic tissue, leading to pancreatic microcirculatory disturbances, causing ischemia and hypoxia in the pancreatic tissue, and ultimately triggering pancreatitis [23].

3.1.2. Infection Causes Pancreatic Tissue Damage:

Infection not only triggers an inflammatory response but may also directly damage pancreatic tissue, disrupting the integrity of pancreatic cells and leading to abnormal activation of pancreatic enzymes [24]. The abnormal activation of pancreatic enzymes is a key factor in the development of AP, as it causes the digestion of the pancreas itself and surrounding tissues, resulting in inflammation and damage to the pancreas [23, 25]. It is noteworthy that in cases of chronic pancreatitis associated with viral hepatitis, HBV is a known cause, and both HBsAg and HCV antigens have been detected in pancreatic tissue, suggesting that chronic infection with HBV or HCV may also have an impact on the pancreas [26].

3.2 Mechanisms of biliary system disorders and microcirculatory disorders

3.2.1 Bile Leakage Causing Disorders

After liver resection, the integrity of the biliary system may be compromised, leading to the complication of bile leakage. According to statistics, the incidence of bile leakage ranges from 4.0% to 17%, posing a serious threat to patients' health [27-29]. Once bile flows into the peritoneal cavity, it not only damages the normal host defense mechanism but may also lead to severe consequences such as sepsis, liver failure, AP, and even death [29]. In particular, components like bile acids in bile are irritants that can act on the pancreatic duct, potentially causing pancreatic duct spasms and subsequently increasing the pressure within the duct. This increased pressure obstructs the normal drainage of pancreatic juice, causing pancreatic enzymes to accumulate and be activated within the pancreas, ultimately triggering AP [30, 31].

To prevent intraoperative bile leakage, the bile leakage test is widely used in clinical practice [32]. This test detects whether the stump of the bile duct on the surface of the transected liver is adequately closed by increasing biliary pressure, which is of great significance for identifying leakage sites and promptly suturing them. However, the bile leakage test may also carry some potential risks. If the biliary pressure is too high, it may lead to biliary venous reflux and cholangitis [33]. Additionally, the White test, as a method for detecting bile leakage, although having certain application value, may also produce adverse reactions and even cause severe AP in specific situations (such as when the distal end of the cystic duct is implanted) [12].

3.2.2 Toxic effects of bile acids on the pancreas

Bile acids, as a class of biomolecules with complex physiological functions, normally participate in the processes of fat digestion and absorption. However, when they abnormally reflux into the pancreatic duct, their potential toxic effects gradually become apparent [34]. Bile acids interact with calcium ions within the pancreatic duct, forming bile acid-calcium complexes. This process not only alters the stability of the pancreatic duct's internal environment but may also further activate pancreatic enzymes, such as trypsin and pancreatic lipase. The abnormal activation of these enzymes is one of the key steps in the onset of pancreatitis [35]. The activation of pancreatic enzymes leads to self-digestion of the pancreas, disrupting the normal structure of pancreatic tissue and triggering a series of inflammatory responses.

In addition to forming complexes with calcium ions, bile acids also exert their toxic effects by directly binding to receptors on the pancreatic cell membrane. There are various receptors present on the pancreatic cell membrane, some of which are highly sensitive and specific to bile acids. When bile acids bind to these receptors, they trigger intracellular signaling pathways, leading to a sharp increase in intracellular calcium ion concentration [35, 36]. Calcium ions serve as important second messengers within cells, and changes in their concentration directly affect cellular physiological functions and metabolic states. The elevation of intracellular calcium ion concentration activates a series of signaling molecules related to cellular damage and inflammatory responses, such as protein kinases and

transcription factors, ultimately resulting in damage to pancreatic cells, including cell membrane rupture and organelle dysfunction.

Furthermore, the activation of intracellular signaling pathways induced by bile acids also promotes the release of inflammatory cytokines, such as tumor necrosis factor and interleukins [37]. These inflammatory cytokines play a crucial role in the pathogenesis of pancreatitis. They not only exacerbate the damage to pancreatic tissue but also attract a large number of inflammatory cells to infiltrate, leading to the typical pathological changes observed in pancreatitis.

3.2.3 Changes in Hepatic Microcirculation and Impaired Pancreatic Microcirculation

During surgery, significant changes occur in the hemodynamic status of the liver, with the status of portal vein blood flow being particularly critical. As the main blood supply vessel to the liver, the portal vein's blood flow directly relates to the liver's function and metabolic status. Controlling intraoperative bleeding is a core aspect of liver resection, crucial for ensuring surgical success and patient safety. Clinically, the Pringle maneuver, a commonly used method of blood flow occlusion, is widely applied in liver resection to control bleeding [12, 38]. However, this method is not without flaws; its greatest drawback is the potential for causing portal vein congestion [39]. Portal vein congestion not only affects the liver's metabolic and detoxification functions but may also have profound effects on the pancreas.

When portal vein blood flow is obstructed or stagnated, the liver experiences congestion, which subsequently impairs its metabolic and detoxification capabilities [40, 41]. As a vital detoxification organ in the human body, once its function is compromised, the liver can no longer effectively eliminate toxins and inflammatory mediators from the body [42]. These harmful substances can reach the pancreas through the bloodstream, stimulating and damaging pancreatic tissue, thereby triggering pancreatitis [43]. The onset of pancreatitis not only leads to the destruction of pancreatic tissue but may also trigger a series of severe complications, endangering the patient's life. Additionally, portal vein congestion can obstruct the blood return to the pancreas [44]. The pancreas, being a highly vascularized organ, relies on proper blood return to maintain the normal metabolism and function of pancreatic tissue. When portal vein congestion occurs, the blood return to the pancreas may be impeded, leading to ischemia and hypoxia in the pancreatic tissue. However, the risk factors for salivary-type hyperamylasemia after liver resection are still under investigation, with liver function and the extent of liver resection possibly being more important influencing factors, rather than just the elevation of portal vein pressure caused by the Pringle maneuver [45]. This perspective reminds us of the need to consider multiple factors comprehensively in clinical practice to more thoroughly assess patient risk and prognosis.

3.3 Mechanisms of oxidative damage and metabolic disorders

3.3.1 Increased oxygen radical production and impaired antioxidant defense mechanisms

After liver resection, the body often enters a state of stress, which serves as a natural response to surgical trauma. In this state, the production of oxygen radicals significantly increases [46]. Oxygen radicals are highly reactive molecules that, due to their strong oxidizing properties, indiscriminately attack molecules within the biological body, including unsaturated fatty acids in the pancreatic cell membrane. This attack triggers a lipid peroxidation reaction, a chain reaction that leads to the destruction of the cell membrane structure, thereby affecting its integrity and function. Once the pancreatic cell membrane is damaged, enzymes within the cell lose their constraints and are released into the extracellular environment. These enzymes include pancreatic enzymes, which normally play a digestive role inside the pancreas. However, when they are abnormally activated and released into the pancreatic tissue or bloodstream, they can trigger a series of inflammatory reactions, ultimately leading to the development of pancreatitis [47, 48].

In addition to direct damage to pancreatic cells, surgical trauma and stress responses can also weaken the body's antioxidant defense mechanisms [49, 50]. The antioxidant defense mechanism is a series of enzymatic and non-enzymatic systems used by the body to combat damage from free radicals such as oxygen radicals. Among these, superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) are two important antioxidant enzymes. Under stress conditions, the activity of these enzymes decreases, making it impossible to effectively eliminate the accumulated oxygen radicals in the body. This results in a large accumulation of oxygen radicals in the body, further exacerbating oxidative damage to the pancreatic tissue, creating a vicious cycle [51].

To explore methods for reducing the incidence of AP after liver resection, Kubota et al. adopted the Pringle method of blood flow occlusion during major liver resection surgeries and simultaneously blocked the superior mesenteric artery [45]. The purpose of this approach was to eliminate arterial blood flow to the organs in the portal venous circulation, preventing an increase in portal venous congestion, and potentially reducing the surgical impact on the pancreas. Subsequently, other researchers delved deeper into this issue by studying oxidative markers. They discovered that the generation of reactive oxygen species (ROS) during blood flow occlusion using the Pringle method was associated with the occurrence of concurrent AP [52].

This suggests that the production and accumulation of ROS may be one of the important factors contributing to the development of AP after liver resection. Furthermore, Varsos et al. conducted further research on the mechanism of pancreatic injury after liver resection using a pig mod e[53]. They found that ROS in the liver can "spill over" after liver resection, reaching the pancreatic tissue through the bloodstream and causing remote oxidative damage. This damage leads to pancreatic cell death and the onset of inflammatory reactions, ultimately resulting in postoperative concurrent AP. They concluded that the ROS generated during liver resection are the main cause of portal venous congestion and the development of AP.

3.3.2 Metabolic and immune disorders caused by liver dysfunction

Studies have shown that the incidence of AP among patients with acute liver failure (ALF) ranges from 6% to 41% [54-56]. In the state of liver failure, the liver's metabolic function is severely impaired, making it unable to normally synthesize and metabolize various nutrients and hormones, which in turn triggers a series of chain reactions of metabolic disorder in the body. Specifically, the liver's ability to synthesize albumin decreases, leading to a reduction in plasma colloid osmotic pressure. This change promotes tissue edema, and the pancreatic tissue is no exception. The edema of the pancreas may then compress the pancreatic duct, affecting the normal drainage of pancreatic juice. The accumulation of pancreatic juice can activate pancreatic enzymes, ultimately triggering the onset of AP [57].

A study delved into this process by constructing a mouse model of acute liver failure (ALF) induced by major hepatectomy [58]. The study found that these mouse models exhibited pancreatic tissue damage and exocrine dysfunction, with incidence rates of hyperamylasemia and hyperlipidemia reaching 5.5% and 20%, respectively. Further research revealed that β-hydroxybutyrate (β-HB) plays a crucial role in protecting the pancreas from ferroptosis following ALF. It acts on the promoter region of ferroptosis-inhibiting genes, inducing the formation of H3K9bhb, thereby effectively preventing the occurrence of AP.

In addition, patients with liver failure often experience abnormal immune function, making them more susceptible to infections. The presence of infection exacerbates the inflammatory response, releasing a large amount of inflammatory mediators [6]. These mediators not only act on the site of infection but may also affect the pancreas, triggering pancreatitis. More severely, the liver is unable to effectively clear endotoxins from the body during liver failure, leading to the development of endotoxemia. Endotoxemia activates immune cells, further releasing inflammatory mediators and triggering systemic inflammatory response syndrome (SIRS) [59]. In this series of complex pathophysiological processes, the risk of AP, as one of the links, increases significantly.

4. Treatment Progress for AP Complicating Liver Resection

4.1 Early Comprehensive Treatment Strategy

In the early treatment stage of AP complicating liver resection, comprehensive treatment measures are of utmost importance.

4.1.1. Fluid Resuscitation

Fluid resuscitation is a critical component in preventing and treating hypovolemia or inadequate organ perfusion. It is recommended to prioritize the use of crystalloid solutions, such as Lactated Ringer's solution, for rapid fluid replacement [60, 61]. The initial infusion rate can be controlled at 5 to 10 mL/(kg·h). For patients with severe hypovolemia or significantly inadequate tissue perfusion, the infusion rate may be appropriately increased or intravenous pressure infusion may be used to ensure adequate blood perfusion.

4.1.2. Nutritional Support

Nutritional support is crucial for the recovery of patients with AP [62]. Enteral nutrition (EN) is considered the preferred method of nutritional support as it helps maintain intestinal barrier function and reduces the risk of infectious complications and multiple organ dysfunction syndrome (MODS) [63]. It is recommended to initiate enteral nutrition within 48 hours after the onset of the disease to meet the patient's nutritional needs as early as possible.

4.1.3. Pain Management

Pain management is an integral part of the treatment for AP[64]. To effectively control pain, a multimodal analgesia strategy is recommended, combining the use of opioid drugs and non-steroidal anti-inflammatory drugs. This approach aims to achieve better pain relief while reducing the side effects associated with single-drug therapy.

In addition, regarding the use of antibiotics, prophylactic antibiotics are not recommended for patients with AP without evidence of infection, in order to avoid unnecessary drug exposure and the development of drug resistance [65]. Regardless of the predicted AP severity, it is recommended that empiric antibiotics should be avoided in patients with AP who lack indications [66].

4.2 Debridement Therapy

For patients with severe AP, surgical debridement of necrotic pancreatic tissue is the preferred treatment method [67]. Guidelines from the American Gastroenterological Association clearly state that, when conditions permit, minimally invasive surgery should be the first choice for debridement of acute necrotizing pancreatitis tissue, rather than traditional open surgical necrosectomy. Minimally invasive surgery offers advantages such as less trauma and faster recovery, which help reduce surgical complications and mortality [68]. Additionally, for patients undergoing debridement therapy, to avoid further multiple organ failure, it is advisable for them to be admitted to the intensive care unit (ICU) after surgery for close monitoring and timely treatment.

5. Conclusion and Future Prospects

In summary, AP that occurs after liver surgery is a rare but serious complication with high mortality rates. The development of this condition involves a complex mix of factors, including infection, inflammatory responses, problems with the biliary system, disruptions in microcirculation, oxidative damage, and metabolic disorders. When an infection happens, it sets off a chain of inflammatory reactions that harm the pancreas's blood flow and tissue structure. Issues with the biliary system can cause bile acids to flow back into the pancreatic duct, activating enzymes and damaging tissue. Additionally, changes in the liver's blood flow and weakened antioxidant defenses contribute to reduced blood flow to the pancreas and increased oxidative stress, raising the risk of AP. Treating AP after liver surgery requires a team approach, with a focus on early and comprehensive management, such as administering

fluids, offering nutritional support, and managing pain effectively. In severe cases, surgical removal of dead pancreatic tissue may be needed, and minimally invasive techniques are preferred over traditional open surgery because they cause less harm and allow for quicker recovery.

Moving forward, future research should aim to understand the underlying causes of AP after liver surgery, especially the roles of bile acids, oxidative stress, and immune system problems. This knowledge will help in developing targeted treatments and prevention strategies. Progress in minimally invasive surgery, care before and after surgery, and personalized medicine offers hope for improving patient outcomes and reducing the occurrence of this serious complication. Furthermore, creating fast and accurate diagnostic systems is crucial for early detection and intervention. Close collaboration among surgeons, gastroenterologists, and intensive care specialists is essential for optimizing the care of patients with AP after liver surgery. Ongoing innovation and research in this area will certainly contribute to advancements in liver surgery and improve the outlook for affected patients.

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