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ORIGINAL

IMPACT OF INTENSE PHYSICAL ACTIVITY IN ATHLETES ON INTESTINAL MUCOSAL INTEGRITY AND ITS ROLE IN ACUTE GASTRIC HEMORRHAGE AND POSTOPERATIVE INFECTION RISKS

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ABSTRACT

In the context of rising gastric disease prevalence, acute gastric hemorrhage presents a significant clinical challenge, particularly among athletes who engage in intense physical activity. This demographic may have unique vulnerabilities due to the stress and strain of their rigorous training and performance routines. Acute gastric bleeding can arise from various sources, including gastritis from Helicobacter pylori infection, gastric ulcers, or vascular abnormalities exacerbated by lifestyle factors like excessive alcohol consumption. However, the impact of high-intensity physical exertion, common in athletes, on these conditions remains underexplored. In athletes, the management of acute gastric bleeding often involves conservative drug therapy post-hemodilation, with proton pump inhibitors like omeprazole offering both anti-inflammatory and acid-inhibiting effects. Surgical intervention is reserved for severe cases, considering the heightened risk of postoperative abdominal infections due to the stomach's unique physiology and its microbial population. This study focuses on the intestinal mucosal barrier's function postoperatively in athletes who have undergone treatment for acute gastric bleeding. We explore how intense physical activity influences intestinal mucosal integrity and its subsequent role in postoperative infection risks. The role of high-mobility group box1 (HMGB1) and the receptor for advanced glycation end products (RAGE) in this context is also examined. HMGB1, a crucial pro-inflammatory cytokine and late inflammatory mediator, and RAGE, a significant HMGB1 receptor, are believed to play pivotal roles in the inflammatory response following acute gastric bleeding. Our research aims to investigate the changes in intestinal mucosal barrier function and the levels of HMGB1 and RAGE in athletes with acute gastric bleeding. This study will provide insights into how physical stressors unique to athletes might affect postoperative outcomes, particularly infection risks. The findings could guide the development of tailored therapeutic and preventative strategies for this specific population.

KEYWORDS: Athletes; Intense Physical Activity; Acute gastric bleeding; Abdominal infection; Intestinal mucosal barrier; High-mobility group box1; Receptor for advanced glycation end product

1. INTRODUCTION

Athletes, through their rigorous training regimens and high levels of physical exertion, push their bodies to extraordinary limits, aiming for peak performance. However, the pursuit of athletic excellence is not without its challenges, and the impact of intense physical activity on various physiological systems is a topic of growing interest and concern. Among the areas of significant importance is the integrity of the intestinal mucosa, a vital barrier that separates the gut's internal environment from the bloodstream. The intestinal mucosa plays a crucial role in nutrient absorption, immune regulation, and defense against pathogens. Any compromise in its integrity can have far-reaching consequences for an individual's health, particularly in the context of athletes. Intense physical activity, such as endurance running, high-intensity training, and competitive sports, places substantial stress on the body, including the gastrointestinal system. This stress has been implicated in the disruption of the intestinal mucosal barrier, potentially leading to increased susceptibility to acute gastric hemorrhage and postoperative infections. This study delves into the intricate relationship between intense physical activity in athletes, the integrity of the intestinal mucosa, and its role in acute gastric hemorrhage and postoperative infection risks. It seeks to unravel the underlying mechanisms by which strenuous exercise may compromise the gut barrier and how this, in turn, contributes to the heightened vulnerability of athletes to these specific health challenges(Commission, 2001; Wang et al., 2020).

The acute gastric hemorrhage observed in athletes has been linked to exercise-induced gastrointestinal bleeding, a phenomenon characterized by the presence of blood in the upper digestive tract during or after intense physical activity. Understanding the impact of exercise on the integrity of the intestinal mucosa is crucial in deciphering the etiology of this condition and devising preventive measures to safeguard athlete health(Liang et al., 2012). Furthermore, the heightened risk of postoperative infections in athletes necessitates an exploration of the gut's role as a potential source of infection. It is essential to elucidate how exercise-induced changes in intestinal mucosal integrity may contribute to the translocation of bacteria and pathogens, which could pose significant risks following surgical interventions, common in sports-related injuries. It is imperative to optimize athlete health and performance by mitigating the risks of acute gastric hemorrhage and postoperative infections while supporting the pursuit of excellence in the world of sports and physical fitness.

2. SUBJECTS AND METHODS

2.1 Subjects

Thirty-six patients with acute gastric hemorrhage who underwent open abdomen and postoperative abdominal infection admitted to our hospital between June 2015 and June 2020 were selected as the infection group, and all of them met the relevant diagnostic criteria in the *Diagnostic Criteria for Nosocomial Infection* (Commission, 2001; Wang et al., 2020). Another 72 patients without postoperative infection during the same period were selected as the non-infection group. Inclusion criteria: (1) met the diagnostic criteria for gastric bleeding in *Gastroenterology* and were found to have vascular outgrowth or active bleeding by endoscopy; (2) age ≥ 18 years; (3) normal coagulation function; (4) complete clinical data. Exclusion criteria: (1) pregnant or lactating women; (2) patients with malignancy; (3) patients with other infectious or immune system diseases; (4) unconscious; (5) patients with significant lesions of organic origin. The study strictly adhered to the principles of the *Declaration of Helsinki*.

2.2 Methods

Clinical data collection Clinical data of patients with acute gastric bleeding, including gender, age, Body mass index (BMI), Helicobacter pylori (Hp) infection, liver cirrhosis, excessive drinking (with the definition of excessive drinking in the *Report on Chronic Disease Risk Factor Surveillance in China* (2010) as a reference (Liang et al., 2012), operative time, diabetes, time of intestinal dysfunction, Pepsinogen (PG1), and CD4+/CD8+ levels were collected.

Detection of intestinal mucosal barrier function and HMGB1 and RAGE levels of peripheral blood Fasting elbow vein blood was collected in the early morning 3 days after surgery, and the supernatant was collected after centrifugation at 3000 r/min for 10 min. Then, the serum levels of DAO, ET and D-lac were determined with the Diamine oxidase (DAO)/Endotoxin (ET)/D-lac kit (D-lac) produced by Beijing Zhongsheng Jinyu Diagnostic Technology Limited by Share Ltd. The serum levels of DAO, D-lac and ET were determined by the o-anisidine colorimetric method, dry chemical enzyme method and the modified azo colorimetric method, respectively. The enzyme-linked immunosorbent precipitation method (ELISA) was used to detect the levels of HMGB1 and RAGE, and the kits were purchased from Shanghai Jianglai Biotechnology Co. And Shanghai Kanglang Biotechnology Co.

2.3 Statistical analysis

SPSS 20.0 software was used to analyze the data, and the measurement data were expressed as ± s. Two groups of independent, normal, chi-square data were used for the independent samples t-test. The count data were expressed as the number of cases (percentage), and χ2 test was used for comparison between groups; univariate analysis of clinical data in relation to postoperative abdominal infection after acute gastric bleeding was performed. Logistic regression was used to analyze the statistically significant factors and to derive independent risk factors for postoperative abdominal infection. The effectiveness of DAO, ET, D-lac, HMGB1 and RAGE levels in predicting postoperative abdominal infection in patients with acute gastric bleeding was analyzed using the receiver operating characteristic curve (ROC). $P< 0.05$ indicates a statistically significant difference.

3. RESULTS

3.1 Univariate analysis of abdominal infection after acute gastric bleeding

Univariate analysis showed statistically significant differences ($P<0.05$) in the comparison of age, operative time, diabetes, time of intestinal dysfunction, PG1, and CD4+/CD8+ levels. See Table 1.

Table 1 Univariate analysis of abdominal infection after acute gastric bleeding [±s, cases (%)]

INFLUENCING FACTORS		THE INFECTION GROUP (36 CASES)	THE NON-INFECTION GROUP (72 CASES)	STATISTICS	*P* VALUE
Gender (cases)	Male	27	50	0.340	0.560
	Female	9	22		
Age (years)	<60	13	41	4.787	0.029
	≥60	23	31		
BMI（kg/m^2）		23.81±2.57	23.57±2.18	0.508	0.613
Hp infection (cases)	Positive	26	57	0.532	0.466
	Negative	10	15		
Liver cirrhosis (Cases)		14	30	0.085	0.770
Diabetes (Cases)		13	10	5.447	0.020
Operative time (min)		84.32±10.57	71.31±9.72	6.368	<0.001
Time of intestinal dysfunction (d)		7.51±1.07	5.24±1.31	8.998	<0.001
PG1 (μg/L)		64.37±12.72	38.42±10.29	11.401	<0.001
CD4+/CD8+		1.18±0.19	1.37±0.24	4.142	<0.001

3.2 Multivariate analysis of abdominal infection after acute gastric bleeding

Logistic regression analysis indicated that operative time, time of intestinal dysfunction and CD4+/CD8+ were independent risk factors for abdominal infection after open surgery for acute gastric bleeding (*P<0.05*). See Table 2.

Table 2 Multivariate analysis of abdominal infection after acute gastric bleeding

INFLUENCING FACTORS	B VALUE	SE	WALD X^2	*P* VALUE	OR VALUE	95%CI
Operative time	1.547	0.723	4.578	0.033	4.697	1.139~19.377
Time of intestinal dysfunction	1.672	0.687	5.923	0.015	5.323	1.385~20.461
CD4+/CD8+	1.438	0.515	7.797	0.005	4.212	1.535~11.558

3.3 Comparison of intestinal mucosal barrier function indexes between the two groups of patients 3 days after operation

3 days after operation, the peripheral blood DAO, ET and D-lac levels of patients in the infection group were significantly higher than those in the non-infection group (*P<0.05*). See Table 3.

Table 3 Comparison of intestinal mucosal barrier function indicators between the two groups 3 days after operation (±s)

INDEXES	THE INFECTION GROUP (N=36)	THE NON-INFECTION GROUP (N=72)	*T* VALUE	*P* VALUE
DAO (U/L)	36.24±10.62	25.27±8.75	5.712	<0.001
ET (U/L)	9.35±3.58	4.82±1.29	9.598	<0.001
D-lac (mg/L)	24.72±6.92	16.34±5.45	6.870	<0.001

3.4 Comparison of peripheral blood HMGB1 and RAGE levels 3 days after operation

3 days after operation, the peripheral blood HGMB1 and RAGE levels of patients were significantly higher in the infection group than in the non-infection group (P<0.05). See Table 4.

Table 4 Comparison of peripheral blood HMGB1 and RAGE levels between the two groups of patients in 3 days after operation

Indexes	The infection group (n=36)	The non-infection group (n=72)	*t* value	*P* value
HGMB1 (μg/L)	30.51±5.72	24.36±4.87	5.832	<0.001
RAGE (μg/L)	7.52±1.65	4.92±1.27	9.054	<0.001

3.5 ROC analysis of peripheral blood DAO, ET, D-lac, HMGB1, and RAGE alone and in combination predicted postoperative abdominal infection at 3 days postoperatively

The AUCs for DAO, ET, D-lac, HGMB1, and RAGE alone and in combination were 0.688, 0.774, 0.721, 0.807, 0.821, and 0.951, respectively, with cut off values of 30.21 U/L, 6.20 U/L, 24.75 mg/L, 26.67 μg/L, and 6.73 μg/L, respectively, with higher AUCs for the combined diagnosis than for the separate diagnosis (P<0.05). See Figure 1, Table 5.

Table 5 ROC analysis of peripheral blood DAO, ET, D-lac, HMGB1, and RAGE alone and in combination for predicting postoperative abdominal infection at 3 days postoperatively

Indexes	AUC	The best cut off values	95% CI	Susceptibility (%)	Specificity (%)	*P* value
DAO	0.688*	30.21	0.574~0.802	71.42	65.78	0.057
ET	0.774*	6.20	0.663~0.884	77.12	78.08	0.056
D-lac	0.721*	24.75	0.614~0.827	50.00	87.50	0.054
HMGB1	0.807*	26.67	0.715~0.900	83.33	75.00	0.047
RAGE	0.821*	6.73	0.740~0.902	88.89	70.78	0.041
Combined forecast	0.951	-	0.902~1.000	86.12	98.44	0.025

Note: *Compared with combined detection, *P<0.05.*

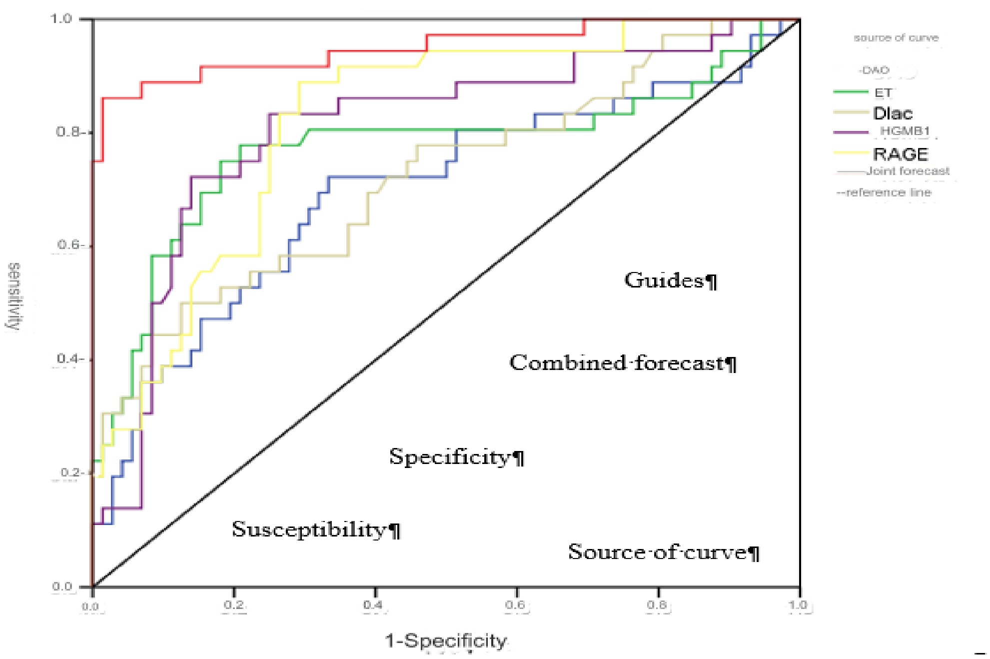

Figure 1 ROC curve of peripheral blood DAO, ET, D-lac, HMGB1, and RAGE alone and in combination for predicting postoperative abdominal infection at 3 days postoperativel

4. Discussion

Acute gastric bleeding, also known as upper gastrointestinal bleeding, is usually caused by ulcers in the stomach and duodenum, etc., and is associated with the fast pace of modern life, dietary habits, and mental and emotional abnormalities (Abed, Alassaf, Jasim, Alfahad, & Qazzaz, 2020; PARK et al., 2000). Also, liver cirrhosis and gastric cancer predispose to cause acute gastric bleeding. As an acute and severe case, acute gastric bleeding has a mortality rate of 2% to 15% if timely and rapid treatment is not provided (Lou et al., 2018). The professional agreement on the emergency diagnostic and treatment procedure is that when patients' bleeding cannot be managed by conservative medication therapy and endoscopic methods, surgery is required (Pei, Song, & Yu, 2017). The risk of postoperative infection, especially endogenous infection, is high due to the abundance of gastrointestinal microbiota (Tsai et al., 2016).

The present study showed that the clinical data such as age, operative time, diabetes, time of intestinal dysfunction and laboratory indexes such as PG1 and CD4+/CD8+ levels in patients with abdominal infection after acute gastric bleeding were statistically different from those in the group without abdominal infection. This is because the impairment of gastrointestinal function in older patients and Hp infection can cause the destruction of the closed abdominal cavity barrier, and additional surgical procedures can exacerbate gastrointestinal function, leading to postoperative intestinal dysfunction. The longer it persists, the more changes in the internal environmental disorder, blood perfusion and inflammatory response will occur, which in turn will lead to intestinal flora disorders, and cause infection (Klingensmith & Coopersmith, 2016). Further multivariate logistic regression analysis revealed that operative time, time of intestinal dysfunction and CD4+/CD8+ were independent risk factors for abdominal infection after acute gastric bleeding, suggesting that a multidisciplinary diagnostic and therapeutic strategy can be used for patients with refractory acute gastric bleeding. Moreover, the bleeding site can be detected early by endoscopic or imaging findings, which can help reduce the incidence and duration of bowel dysfunction, as well as shorten the time to surgery (Lu, Loffroy, Lau, & Barkun, 2014). In addition, it is necessary to pay attention to the immune function status of patients to avoid abdominal infections caused by intestinal flora ectopic (Obata & Pachnis, 2016).

As acute gastric bleeding can lead to restriction of gastrointestinal motility and possibly even toxic intestinal paralysis, surgical hemostasis can cause intestinal mucosa damage, bacterial and ET ectopic, thus causing systemic inflammatory response syndrome or intestinal infection. Lipopolysaccharides on the cell wall, the most abundant bacterial ET in the intestine, can migrate into the circulatory system and develop into endotoxemia as the intestinal mucosal barrier is compromised(Vancamelbeke & Vermeire, 2017). Relevant studies have demonstrated a connection between intestinal barrier function and bacterial ET in the serum. DAO, a highly active enzyme in the epithelial cells of the intestinal mucosa, causes damage to the epithelial cells when the intestinal mucosa is damaged. The blood will then absorb a significant quantity of DAO, leading to a significant rise in DAO. Accordingly, elevated serum DAO levels can be detected when the intestinal mucosa barrier is impaired (Sertaridou, Papaioannou, Kolios, & Pneumatikos, 2015). D-lac is a common metabolite of the normal gastrointestinal flora and cannot be produced or metabolized in other tissues. When the intestinal mucosa is damaged, intestinal D-lac will enter the circulation through the damaged intestinal mucosa, resulting in the elevated peripheral blood D-lac levels, implying a damaged intestinal mucosa barrier (Xie, Cai, & Zhang, 2023). The study showed that the peripheral blood DAO, ET, and D-lac levels of patients in the infection group were significantly higher than those in the non-infection group 3 days after the operation, suggesting that the postoperative intestinal mucosa barrier function of patients in the infection group was more severely impaired, and intestinal flora was more likely to become pathogenic bacteria after entering the abdominal cavity through the damaged barrier, causing infection.

The AUCs of DAO, ET, and D-lac levels in 3 days following surgery, which can predict abdominal infection presenting with acute gastric bleeding, were 0.688, 0.774, and 0.721, respectively, according to additional ROC curve results, with ET having the highest predictive value primarily because the gastrointestinal tract is predominated by gram-negative bacteria and contains more endogenous ET, such as lipopolysaccharide (Al-Judaibi, Chande, Dresser, Sultan, & Gregor, 2010; Karakike et al., 2019). The study showed that the peripheral blood HMGB1 and RAGE levels in the infection group were significantly higher than those in the non-infection group, suggesting that postoperative abdominal infection leads to HMGB1 activation. RAGE, as its receptor, can further promote the release of inflammatory cytokines causing inflammatory organ damage by acting on nuclear factor κB nuclear translocation on a variety of inflammatory cells (Christaki, Lazaridis, & Opal, 2012). Therefore, elevated peripheral blood HMGB1 and RAGE levels may be related to the prediction of postoperative infection. ROC results confirmed that the AUCs of HMGB1 and RAGE levels at 3 days postoperatively predicted postoperative abdominal infection after acute gastric bleeding with the high predictive values of 0.807 and 0.821, respectively (Silva et al., 2020). The combined diagnosis of intestinal mucosa function indexes with HMGB1 and RAGE may further improve the diagnostic value, because intestinal flora is ectopic after the intestinal mucosa barrier function is damaged, which is the main etiology of postoperative infection, and HMGB1 and RAGE participate in the inflammatory response caused by ET (Andersson, Yang, & Harris, 2018; Lalisang et al., 2019). In the study, the AUC of DAO, ET, D-lac, HMGB1, and RAGE after combined diagnosis reached 0.951, significantly higher than each index individually. Therefore, postoperative levels of DAO, ET, D-LAC, HMGB1 and RAGE can be clinically detected in patients with acute gastric bleeding.

The excessively raised signs will suggest that appropriate steps for avoiding and treating stomach infections in patients need to be performed as soon as feasible (Esmaeili, Zareian, Eagderi, & Alwan, 2016; Lederer et al., 2017).

5. Conclusion

In conclusion, the impact of intense physical activity in athletes on intestinal mucosal integrity and its role in acute gastric hemorrhage and postoperative infection risks is a critical area of concern for the sports and medical communities. Our investigation has illuminated the potential risks associated with strenuous exercise on the gastrointestinal system, particularly the disruption of the intestinal mucosal barrier. These findings emphasize the need for heightened awareness of gastrointestinal health in athletes and the development of targeted preventive strategies to mitigate the risks of acute gastric hemorrhage and postoperative infections. By safeguarding the intestinal mucosal integrity, we can better support the long-term health and performance of athletes, ensuring that their dedication to physical excellence is not compromised by preventable health issues. As the world of sports and physical fitness continues to evolve, research and interventions in this area hold the promise of enhancing athlete well-being and enabling them to achieve their goals while minimizing the adverse effects of intense physical activity on their gastrointestinal health.

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