Review Article
Factors influencing feeding intolerance in critically ill patients during enteral nutrition

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Abstract: The symptoms of feeding intolerance, such as bloating, vomiting, diarrhea, and constipation, often occur in critically ill patients during enteral nutrition (EN). Feeding intolerance can affect the effectiveness of EN, thereby prolonging hospital stay, influencing mechanical ventilation, and increasing mortality in critically ill patients. Therefore, gaining a full understanding of the causes of feeding intolerance and adopting appropriate preventive and therapeutic measures to reduce the incidence of feeding intolerance may improve the clinical prognosis in critically ill patients. This study aimed to explore the clinical manifestations of feeding intolerance and the impact of the factors related to disease, endocrine hormones, drugs, and gastrointestinal flora on feeding intolerance. The prevention and treatment measures for feeding intolerance were also investigated.

Keywords: Critically ill patients, enteral nutrition, feeding intolerance, influencing factors

Introduction

When nutrient intake does not meet the body's metabolic demands, it can lead to malnutrition. In critically ill patients, changes in body protein and energy metabolism following surgery, burns, and sepsis may also lead to malnutrition [1]. Enteral nutrition (EN) is the preferred method of providing nutritional support to critically ill patients. It is preferred over parenteral nutrition because of its advantages of simplicity, lower cost, fewer infection complications, and ability to protect intestinal mucosal barrier [2, 3]. However, the feeding intolerance usually occurs during EN, leading to adjustment or discontinuation of the implementation of EN. Feeding intolerance is also associated with the occurrence of pneumonia and prolonged intensive care unit stay [4, 5]. Therefore, fully understanding the causes of feeding intolerance and adopting appropriate prevention and treatment measures to reduce the incidence of feeding intolerance are important to improve the clinical prognosis in critically ill patients. In this study, the clinical manifestations, influencing factors associated with feeding intolerance, and measures for improvement were reviewed.

Results

Clinical manifestations of feeding intolerance in critically ill patients

Bloating and vomiting: Up to 50% of critically ill patients receiving mechanical ventilation have delayed gastric emptying, which is mainly caused by changes in antrum-pylorus-duodenum and intestinal motility [6, 7]. Bloating can often cause increased intra-abdominal pressure, which can affect the movement of the diaphragm, function of pulmonary ventilation, and even renal hemodynamics and perfusion. Vomiting can cause aspiration and increase the risk of aspiration pneumonia. Local pyloric movement increases, antral motility decreases, and the feedback inhibition of gastric emptying by nutrients in the small intestine is enhanced in critically ill patients [8]. Meanwhile, the suppression of gastric activity induced by EN perfusion also occurs in critically ill patients [9, 10]. Further, the integration between the proximal and distal gastric motor functions, which plays an important role in the emptying of food, is also impaired. These factors can cause increased retention time for food in the proximal

stomach, delayed gastric emptying, and eventually bloating or vomiting [11].

Diarrhea and constipation: Diarrhea is a gastrointestinal symptom that often occurs during EN feeding in critically ill patients [12-14]. It is defined as three or more watery stools within 24 h [15]. It can not only affect nutrient absorption but also cause damage to the intestinal mucosa and then the intestinal barrier function, resulting in the passage of intestinal bacteria and toxins into the bloodstream. Constipation is characterized by less than one bowel movement for three consecutive days [16]. Toxins in the intestines cannot be eliminated and are absorbed into the bloodstream in patients with constipation. Excessive intestinal contents can cause increased intra-abdominal pressure, causing aggravation of the disease.

Influencing factors associated with feeding intolerance in critically ill patients

Diseases associated with feeding intolerance: Critically ill patients often experience stress-induced hyperglycemia due to the severity of the patient's illness. Hyperglycemia can delay gastric emptying by affecting antral contraction. Therefore, feeding intolerance often occurs in critically ill patients when blood glucose levels are too high [17]. In patients with traumatic brain injury (TBI), axonal injury in the autonomic nervous system induced by increased intracranial pressure can cause gastrointestinal motility disorders [18]. A study found that during the early period of EN, increased gastric residuals were present in 65.2% of patients with TBI often accompanied by abnormal gastrointestinal motility [19].

Endocrine hormones associated with feeding intolerance: Gastric motility disorders are closely associated with the plasma concentrations of cholecystokinin (CCK) and peptide tyrosine-tyrosine (PYY) in critically ill patients [20]. CCK is secreted by I cells in the small intestine. It stimulates gallbladder contraction and pancreatic enzyme secretion, promotes fat and protein digestion, but inhibits gastric motility. Plasma CCK concentrations were found to be higher in critically ill patients. Also, the sensitivity of the gastrointestinal tract to CCK increased, thereby leading to delayed gastric emptying [21, 22]. PYY is mainly secreted by L cells of the colon and rectum. It can also be secreted by endocrine cells within the stomach and pancreas. It has an inhibitory effect on gastrointestinal motility and appetite. Plasma PYY concentration is significantly increased in critically ill patients, leading to gastrointestinal motility dysfunction [20].

Both ghrelin and motilin are hormones released by epithelial cells of the upper digestive tract. They increase appetite and regulate migrating motor complex in the interdigestive state. Reduced plasma ghrelin concentration can lead to gastroesophageal reflux disease, gastritis, and functional dyspepsia [23-25]. A study found that critically ill patients had abnormally low motilin levels, leading to the development of feeding intolerance [26].

Drugs associated with feeding intolerance: Some drugs such as sedatives and analgesics and vasoactive drugs administered to critically ill patients can potentially affect gastrointestinal motility. Analgesics, such as opioids, can affect the movement of the upper gastrointestinal tract through the central and peripheral opioid receptors in the gastrointestinal tract. They can cause retroperistalsis in the duodenum, antral contraction, and delayed gastric emptying by reducing gastric tension [27]. Sedatives, such as propofol, can delay gastric emptying, increase gastrointestinal transit time, and affect the gastrointestinal motility in a dose-dependent manner. Benzodiazepine drugs, such as midazolam, are also commonly used sedatives in the clinic. They increase gastrointestinal transit time [28]. The motor function of the gastrointestinal tract is also regulated by adrenergic and dopaminergic nerves. Catecholamines, such as norepinephrine, adrenaline, and dopamine, can affect gastrointestinal motility, leading to feeding intolerance [29]. In addition, erythromycin is a macrolide antibiotic that can promote gastric movement and gastric emptying. High doses of erythromycin can restart gastric movement in critically ill patients during acute episodes of gastric stasis retention, but it may also cause vomiting and diarrhea [30].

Gastrointestinal flora associated with feeding intolerance: More than 10,000 different species of bacteria live in the gastrointestinal tract of the human body; of these, more than 90% are Firmicutes and Bacteroides [31]. The gas-

trointestinal tract provides an ideal environment for microbial flora. This complex ecosystem protects the body from pathogens. The balance in the gastrointestinal microbiota plays an important role in maintaining gastrointestinal function. Broad-spectrum antibiotics are often used to prevent infection in critically ill patients. However, these antibiotics can induce an imbalance in gastrointestinal flora and cause gastrointestinal dysfunction, which manifests as feeding intolerance.

Prevention and treatment measures for feeding intolerance

Drug treatment: Delayed gastric emptying is one of the main causes of feeding intolerance. Hence, drugs can be used to promote gastric emptying and improve tolerance in critically ill patients. Metoclopramide and domperidone are both dopamine receptor antagonists commonly used to treat feeding intolerance. Metoclopramide can promote gastrointestinal motility by blocking dopamine receptors on the medullary chemoreceptor trigger zone and gastrointestinal tract and improve feeding intolerance in critically ill patients. However, long-term use of metoclopramide can cause rapid tolerance. Therefore, an intravenous injection of erythromycin can be used to increase the effect of metoclopramide in promoting motility and reduce the rapid tolerance caused by metoclopramide. However, metoclopramide is contraindicated in patients with TBI because of the increased intracranial pressure after application [32]. Domperidone selectively blocks peripheral dopamine receptors, suppresses the inhibitory effect of dopamine on post-synaptic cholinergic neurons in the myenteric plexuses of the gastrointestinal tract, promotes acetylcholine release, coordinates and enhances gastrointestinal motility, and promotes gastric emptying. It does not cross the blood-brain barrier, and has no extrapyramidal reaction compared with metoclopramide [33]. 5-Hydroxytryptamine (5-HT) is a monoamine neurotransmitter that acts on the 5-HT receptor in the gastrointestinal tract and stimulates gastrointestinal motility. 5-HT4 receptor agonists, such as mosapride, promote the release of 5-HT and acetylcholine in the enteric nervous system, improve gastric emptying, and reduce the occurrence of EN in critically ill patients by activating the 5-HT4 receptor and parasympathetic nervous system on the myenteric plexuses of the intestinal wall. Mosapride does not cause extrapyramidal reactions [34].

Optimizing methods of EN: Critically ill patients have a high risk of aspiration and aspiration pneumonia during EN. Long-term supine position and the head of the bed less than 30° during EN are more likely to cause the aspiration of gastric contents [35]. Hence, the head of the bed should be maintained at 30° and 45° during EN feeding to minimize aspiration.

If vomiting and aspiration occur in critically ill patients who receive EN via the gastric route, post-pyloric tube feeding can be selected. A previous study found that compared with gastric feeding, post-pyloric feeding could meet the nutritional requirements and reduce gastric residue [36]. Post-pyloric feeding can also reduce the incidence of aspiration and aspiration pneumonia and improve gastrointestinal dysfunction [37].

To improve the feeding tolerance in critically ill patients, the perfusion rate of the nutrient solutions can be appropriately adjusted and the temperature can be appropriately increased during EN. EN formulations can also improve feeding tolerance. Soluble dietary fibers in the nutrient solutions can inhibit gastric emptying, while insoluble dietary fibers can stimulate gastrointestinal motility and promote digestion [38, 39]. Therefore, the use of soluble dietary fibers can reduce the incidence of diarrhea, while the use of insoluble dietary fibers can improve constipation in critically ill patients.

Other treatment measures: Traditional Chinese medicine such as nasogastric feeding of raw Rhubarb powder, mirabilite umbilicus compress, enema feeding of dachengqi decoction, and acupuncture points can also achieve certain effects in critically ill patients who are likely to develop feeding intolerance [40-42].

Discussion

In summary, the causes of feeding intolerance in critically ill patients include factors associated with the disease itself and the treatment factors. Understanding these influencing factors and adopting appropriate measures can prevent and treat EN feeding intolerance, improve gastrointestinal function, and enhance

the tolerance of critically ill patients to enteral feeding, thus achieving the aim of increasing enteral nutrition supply and promoting the recovery from disease.

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