Review Article

Acute Post-Operative Pain and Gut Microbiota; Is There Any (Clinical) Relationship?

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Abstract

Gut microbiota are the primary focus for a number of active research fields; one of their main areas of effect seem to be their effects on acute pain. Though it is generally realized that development of gut microbiota is after birth, the initial microbial core originates from maternal microbiota in fetus life, rapidly colonizing to adulthood microflora in 3-5 years. Understanding the crosstalk between microbiota, changes in gut flora and post-operative pain, and recognizing the underlying mechanisms are novel fields of study.

Keywords: Gut microbiota; pain; cellular and molecular mechanisms

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Introduction

Gut microbiota

The body microorganisms, which are also called microbiota, lied mainly in the gut, other mucous membranes and skin. It is generally believed that microbiota develops after birth. However, the initial microbial core originates from maternal microbiota in fetus life, and the gut colonized rapidly to adulthood microflora within the first 3-5 years (1). The physiological functions of microbiota include defense against pathogens, providing nutrients such as vitamin B12, folate, and vitamin K, and modulating gut integrity and permeability, which could consequently affect the function of the immune system (2).

The fermentation of indigestible carbohydrates by bacteria in the colon produces rapidly absorbed short chain fatty acids (SCFAs). SCFAs play an important role in the modulation of gene expression, cellular differentiation, proliferation and apoptosis, metabolism of lipids and glucose in liver, and regulation of different immune cells and inflammatory responses (3, 4). SCFAs bind to a member of G-protein-coupled receptors, GPR43. Experimental models of colitis, arthritis and asthma showed that both GPR43-deficient and germ-free mice manifested intensified or unresolving inflammation (5). The production of SCFAs in healthy people depends on dietary factors and substrate availability, intestinal transit time, and microbiota composition and species (6). Some bacteria could produce neuroactive substances including gamma-aminobutyric acid (GABA), serotonin, catecholamines, histamine, and

acetylcholine. These metabolites not only could affect neurophysiology of brain development and behavior, but could also regulate gastrointestinal, cardiac, respiratory, and endocrine functions through direct interaction with gastrointestinal receptors or entering into the circulation (7, 8).

The effects of gut microbiota could partly occur through small non-coding RNA molecules called microRNAs. It has been demonstrated that microRNAs could modulate host gene expression and gut flora could reciprocally affect host microRNA expression (9). Moreover, fecal microRNAs could modulate gut flora by targeting bacterial gene expression and growth (10). MicroRNAs are major contributors of the immune system and also, a number of disease states; including the clinical conditions in the perioperative period (11, 12). The regulation of microRNAs by microbiota could affect intestinal epithelium and play an important role in the pathogenesis of disorders like inflammatory bowel disease (13).

Despite relatively stable microbiota during life, different illnesses, surgeries, medications, dietary factors, and lifestyle changes could contribute to the imbalance of body microorganisms, or dysbiosis, and many gastrointestinal and extra-gastrointestinal disorders (1). For example, clinical and experimental studies showed that gut microbiota change in obesity. An increase in the *Firmicutes* and decrease in the *Bacteroidetes*, two dominant bacterial divisions have been reported in obese state (14, 15). These alterations could be associated with changes in the metabolic function of microbiota including higher capacity to absorb energy of nutrients (15). In addition, it has been shown that intestinal microbiota is considerably different in children with typical western diets rich in fat and sugar compared to those in rural communities consuming foods rich in fiber. There was a higher richness and biodiversity in microbiota, but reduced pathogenic strains with high fiber diets (16). Dietary fats, especially the saturated types, can change the composition of bile acids and gut flora, which in turn can cause dysbiosis and affect the immune function of the host (17). Stress could also substantially affect gut physiology and microbiota through reducing the beneficial *Lactobacillus* strain and increase pathogens like *E. coli* (18). Antimicrobial therapies affect the abundance and function of gut microbiota, which may lead to long-term dysbiosis and consequent disorders (19).

The role of gut microbiota in the perioperative period diseases

Previous studies have mainly focused on the role of microbiome diversity and abundance in chronic disorders including obesity, diabetes, intestinal disorders such as inflammatory bowel disease, irritable bowel syndrome (IBS), and colorectal cancer. The role of gut flora, and especially probiotics, has been considered recently in critical care. Probiotic refers to live nonpathogenic microorganisms, most commonly Lactobacillus and Bifidobacterium, that their sufficient amounts exert many health benefits through recovery of gut microbial balance (20). During critical illness, many factors could disturb the normal physiologic gut microbiota. The trauma or disease induced stress, along with medications like antibiotics, catecholamines and histamine H2 receptor blockers, and other supportive treatments such as artificial respiration might be involved (21). Remarkable alterations in the gut flora are also seen in digestive surgeries due to bowel cleansing (22). Many surgeries are accompanied with pre- and post- fasting state as a part of treatment or insufficient nutrition support. The direct effects of starvation on gut microbiota in critical conditions are not still well described. However, it has been observed that undernutrition in children and anorexia nervosa in young adults are associated with substantial changes in bacterial diversity and abundance (23, 24).

Gut microbiota and pain (acute and chronic)

The clinical effects of interventions on microbiota have been assessed in different types of major abdominal surgeries including liver transplantation, hepatectomy, and other organ resections. These studies mainly evaluated outcomes including immune function and infectious complication, antibiotic-associated diarrhea, epithelial permeability, duration of antibiotics use, and duration of hospital stay (21, 25).

Post-operative pain is one of the most important complications in surgical patients. Few data is available on the relationship of this kind of acute

pain with gut microbiota and the effect of relevant interventions. However, the effect of gut microbiota as a key regulator of visceral pain has been stated recently. Visceral pain is referred to pain from internal organs such as abdomen, thorax or pelvis and is most prevalent in functional gastrointestinal disorders (26). Many animal studies have confirmed the involvement of gut microbiota on visceral pain. For example, it has been reported that germ-free mice showed visceral hypersensitivity. Besides, an increased gene expression of Toll-like receptors and cytokines in the spinal cord, and structural changes in brain areas responsible for pain perception were observed. Visceral hypersensitivity, pain threshold and many other mentioned disorders were reversed following microbial colonization (27). Interestingly, it has been observed that visceral hypersensitivity can be transferred from fecal microbiota of patients with IBS to germ free rats (28).

These findings suggest a promise in managing perioperative pain in patients. In other words, preventive or therapeutic strategies are designed to ameliorate perioperative pain based on the interactions of gut microbiota on pain inducing mechanisms; these strategies though till a bit premature, could be a real promise in finding novel therapeutic approaches in pain management; both for acute and chronic pain. Some of these new perspectives are discussed in the next paragraphs (29-36).

Acute post-operative pain is among the most common and at times, intractable clinical challenges; with a number of therapeutic modalities being used for its management; however, a considerable number of patients suffer acute postoperative pain despite all these efforts; leading to both psychological burden and aftermath of physiologic or pathologic stress response due to acute pain. Though pharmaceutical agents are used as the main armamentarium in acute pain management, they lack complete efficacy in resolving acute pain; meanwhile, there are associated with a number of undesirable side effects which some of them are really major events. During the last decades, a larger number of acute pain studies have been involved to finding new treatments and during the recent years, there are studies exploring the considerable efficacy of modulating gut microbiota in alleviating acute postoperative pain (37-41).

Implications for future studies

Understanding the crosstalk between microbiota, changes in gut flora and post-operative pain, and recognizing the underlying mechanisms are novel fields of study. The potential clinical benefit of using probiotics in the management of acute pain is also of importance. Despite, differences in the nature of visceral and post-operative pains, it has been observed that some probiotics could relieve stress induced visceral pain in rodents. After 14 days oral gavage of three different probiotic strains, Bifidobacterium infantis 35624 decreased visceral pain behaviors in rats with colorectal distension (42). Oral Lactobacillus farciminis had similar antinociceptive effect in rats following colorectal distension and prevented stress induced hypersensitivity (43). A systematic review of clinical studies showed that specific probiotics could affect abdominal pain in some patients with IBS. Moreover, 21 days supplementation with the probiotic Lactobacillus acidophilus NCFM increased the mRNA and protein expression of mu-opioid receptor in women with mild to moderate abdominal pain. Combination of Lactobacillus acidophilus NCFM with Bifidobacterium lactis Bi-07 decreased the number of days with abdominal pain significantly (44).

It should be considered that the effects of probiotics are strain and formulation specific and varies from one to another. Thus, the clinical efficacy could not be extended to other pathophysiological conditions such as post-operative surgery. The safety and dosage of administration should be determined in each disease separately. Thus, further well-designed experimental and clinical studies are required to investigate the interaction between gut microbiota and acute post-operative pain, and the efficacy of probiotic supplementation.

Conclusion

The results of recent researches open new windows to management of pain through manipulation of gut microbiota. These results are wide and still need further assessment for clinical applicability.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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