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LETTER TO THE EDITOR

Perioperative Dysbiosis: Rethinking the Anaesthetic Contribution to Postoperative Outcomes via the Human Microbiota

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Abstract

The gut microbiome plays a crucial role in perioperative care. Surgical stress and anaesthesia disrupt the balance of intestinal flora, known as dysbiosis, which can affect gut health and metabolism. Pain relievers like morphine and certain anaesthetics contribute to this imbalance. Dysbiosis may also lead to memory loss and cognitive issues post-surgery. Future studies aim to use probiotics and beneficial substances to improve health and prevent cognitive decline.

Key words: Dysbiosis; Microbiota; Anaesthetics; Postoperative outcome.

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Dear Editor,

Patients who have surgery face drugs and experience great physical stress during the perioperative phase. Modern anaesthesiology seeks to control the patient's condition safely and reversibly, but this requires a thorough evaluation. It is imperative to thoroughly investigate the physiological effects of the anaesthetic approach and other therapies on the complex inner systems of the patient.[1] There is a crucial though occasionally transient effect of general anaesthesia (GA) and associated therapies on the human body and especially the brain.[2, 3] Dysbiosis refers to the change in the microbiota brought about by medications, which was found to have a considerable effect on several postoperative aspects, including immunological, neurocognitive and others. We treat conditions, dysfunctions and other chronic pain issues.[4, 5]

Host activities, including metabolism, neurological control and immune system development, the complicated gut microbiota, comprising billions of bacteria, is vital. The intricate, two-way link between the gut and the central nervous system

(CNS), known as the microbiota-gut-brain axis (MGB),[6] helps to regulate this great effect.

Because of increased contact, perioperative neurocognitive disorders (PNDs), like postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are becoming more common among variations along the MGB axis. Studies have revealed an association between the transient cognitive impairments caused by surgery and anaesthesia, with poor outcomes seen in the gut flora of aged mice, along with related faecal metabolites.[7-9]

One primary mechanistic link is the control of tryptophan metabolism by microbes. Commensal gut bacteria transform tryptophan into defensive, anti-inflammatory metabolites like indole-3-propionic acid (IPA). However, surgical stress and anaesthesia might reduce the diversity of these beneficial bacteria. This reduction prevents the tryptophan metabolic path, producing lower concentrations of neuroprotective substances and greater amounts of pro-inflammatory markers (such as IL-6 and IL-1β) within the central nervous system (CNS). This mechanism thus supports neuroinflammation and cognitive impairment.[10] An inverse relationship exists between baseline plasma isopropyl alcohol levels and subsequent start. Clinical investigations have proven the existence of postoperative delirium. Preclinical models have supported this connection with IPA treatment, demonstrating a protective action against postoperative cognitive impairment (POCD).[11, 12] While fasting, surgical stress and mandatory antibiotic prophylaxis are clearly significant dysbiosis causes in the perioperative setting. There is more data other perioperative stressors can also help; some anaesthetic substances are independent modulators of microbial structure and activity.[2, 13]

Preclinical investigations mostly on rodent models have shown that volatile compounds like isoflurane or sevoflurane, for four hours of exposure, change the composition of gut flora significantly and often long-lastingly, which may result from isoflurane or sevoflurane. The usual outcome of these changes is a decrease in both the abundance and diversity of gut microorganism species.[14, 15] Obligate anaerobes decline significantly. Anaerobic bacteria, particularly those from the phylum *Firmicutes* and the order *Clostridiales*, which includes *Lactobacillus* and *Clostridium* cluster IV producing short-chain fatty acids (SCFAs), are notably affected.[16] A marker of a Gram-negative bacterium's evident rise, particularly those belonging to the *Proteobacteria* and *Actinobacteria phyla (Escherichia–shigella*), is an unstable microbiological state that encourages inflammation.[15]

These changes that continue for weeks after exposure (7 to 14 days or more) reflect a significant change in the gut surrounding for an extended period. Additionally, exposure to isoflurane during the neonatal period has been shown to cause lasting dysbiosis throughout childhood, raising concerns about its potential effects on neurodevelopment.[17]

Research shows that propofol, the intravenous anaesthetic used in total intravenous anaesthesia (TIVA), can alter the gut bacteria in animal models. Specifically, propofol infusion can lead to a decrease in the *Lactobacillus* and *Prevotella*, suggesting the potential change in microbial populations attributed to a broader pharmacological class effect rather than only to volatile anaesthetics. Studies showed that local anaesthetics, such as lidocaine, have an immediate antibacterial effect on the oral microbiome. This can disrupt the balance of the microbiome, potentially leading to health consequences.[18, 19]

The precise processes behind anaesthetic-induced microbial alterations are intricate and include the direct pharmacological effect and indirect physiological modifications brought about by the host.

1. Translocation and a compromised intestinal barrier

Intestinal permeability can be increased due to surgical stress and anaesthetic drugs that directly impair the integrity of the intestinal epithelial barrier (ie induce a leaky gut).[20] Lipopolysaccharides (LPS) and other bacterial products are moved from the intestinal lumen into the bloodstream via this breakdown. Systemic exposure to these microbial-associated molecular patterns (MAMPs) causes a potent, low-grade inflammatory condition, a crucial underlying process for several postoperative sequelae.[20, 21]

2. Niche change and direct antimicrobial action

Certain anaesthetic drugs may have a modest, intrinsic antimicrobial effect that selectively targets helpful, obligate anaerobic bacteria, which are typically more susceptible to xenobiotic exposure.[2, 22] The functional depletion of beneficial

bacteria greatly restricts the competitive overgrowth of opportunistic or pathogenic species (such as *Proteobacteria*), which causes the ensuing ecological vacuum. Creating essential metabolites, such as SCFAs, is crucial for immune control and the health of colonocytes.[23]

3. Disruption of the host's metabolic loops

It is well known that anaesthetics can disrupt host metabolism, particularly the enterohepatic circulation and the microbial conversion of bile acids.[24] The gut microbiota provides the enzymes necessary for deconjugation and producing secondary bile acids. Dysbiosis modifies the bile acid profile and as bile acids are essential signalling molecules, any change in them results in a vicious cycle by selectively encouraging the development of some harmful bacteria, resulting in a more adverse situation, inducing inflammation via the gut-liver-brain axis.[24, 25]

The relationship between dysbiosis caused by anaesthesia and negative outcomes is changing the conceptual framework of postoperative recovery from a sterile surgical event to a systemic, microbial-mediated disease process. Microbiota in gut plays a significant role in regulating the perception and intensity of pain via the gut-pain axis.[5] Loss of essential bacteria reduces SCFA synthesis, lowering pain perception and severity. Bacteria can also make hosts more susceptible to pain. Typical perioperative use of opioid analgesics is a considerable additional source of difficulty, as they are known to directly cause dysbiosis and hurt the intestinal barrier, which has the potential to alter their metabolism and effectiveness.[26] Such microbial conditions might also impact various perioperative medications' pharmacological effects and pharmacokinetics, resulting in erratic concentrations and therapeutic outcomes.[27]

The microbial changes characterised by epithelial barrier dysfunction and loss of diversity all severely compromise the patient's immune resistance.[28] Combining various perioperative tools (fasting, antibiotics, anaesthetics) in studies showed that the resultant dysbiosis significantly reduces the host's ability to respond to a subsequent inflammatory challenge, lowering survival rates.[29] Increased risk of postoperative infections and increased inflammatory morbidity strongly support that the anaesthetic procedure may be a factor. Incorporating microbial science into perioperative medicine represents a paradigm change in preventive and treatment aimed at reducing anaesthetic-related adverse effects.

The deliberate use of probiotics (live beneficial bacteria) and prebiotics (selective substrates) is the easiest intervention to implement.[30] According to preclinical and early-phase clinical evidence, the strategic use of probiotics and prebiotics can help treat a variety of conditions,[31, 32] demonstrating that the targeted administration of particular strains, such as *Lactobacillus*, can alleviate dysbiosis brought on by anaesthesia/surgery, lower neuroinflammation and lessen delirium-like behaviour. The best strain specificity, dosage and delivery timing to successfully combat perioperative dysbiosis's quick, individualised character[30] continue to be a crucial challenge.

An interesting but still experimental approach for quickly replacing a good microbial population and reversing severe or recalcitrant diseases is faecal microbiota transplantation (FMT) to neutralise the bad results of dysbiosis.[33] A customised treatment strategy based on the patient's microbial profile should guide the anaesthesiology course. This requires the following actions:

1. Preoperatively profiling a patient's initial metabolic and microbial condition using cutting-edge sequencing methods aids in the detection of any underlying illnesses.
2. Microbial risk categorisation helps to locate those at high risk for and vulnerable to dysbiosis-induced problems, such as the elderly or those with underlying gastrointestinal disorders.
3. Choosing anaesthetic chemicals (such as TIVA versus volatile) according to their known or expected lowest effect on the patient's individual microbial profile.
4. Minimising the influence of all perioperative variables, including correct antibiotic use, better fasting routines and careful stress management, temperature and supplemental oxygen,[33] helps to maximise co-interventions.

Substantial evidence supports the theory that the human gut microbiota is a critical organ system affecting a patient's healing ability and maintenance throughout surgery and anaesthesia. The primary source of poor results is perioperative dysbiosis, a combination of surgical stress, antibiotic use and the direct effects of surgery and medications used for anaesthesia. The results

are especially postoperative depression and a weakened immune system.[3,7] It is vital to consistently apply preclinical results to direct strong, personalised clinical practice employing multiomics techniques in thorough human translational experiments. Employing a microbiome-centric approach will enable anaesthesiologists to create original preventive and therapeutic approaches that significantly improve surgical patients' long-term results and safety profile.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper .

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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