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Review Article

Going Back to the Future: Anesthesia and the Human Gut Microbiome

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ABSTRACT

Anesthesia in patient care, both in the perioperative period and in the pain clinic, is a challenging field to engage with - this is secondary to the fact that patients are individuals who are influenced by numerous factors, including the bacterial makeup of their microbiome and its parts. With the focus on personalized medicine as the next frontier, this narrative literature review looks at the current trend in individualized medicine, specifically regarding the use of the microbiome and artificial intelligence in the choice of different drugs for the induction and continuation of surgery as well as the management of pain syndromes in patients. This review also includes a summary of the different research directions that can take place based on the most recent data, including microbiome composition testing, therapeutic alterations, and the use of artificial intelligence to select the best drugs for treating the patient.

Introduction

Hippocrates is quoted as saying, “let food be thy medicine and medicine be thy food” [1]. This singular line demonstrates the link between the human gut, the chemicals and flora within it, and the effects that this axis has on all of human health. While a simple kernel of truth was contained within this idea, the complexity of the situation is far greater than Hippocrates could have imagined. The human microbiome is a complex genome network of thousands of species of microorganisms, consisting of bacteria, viruses, fungi, and archaea, which has been heavily studied for its impact on human health [2-6]. This microflora population exists within numerous body systems, including the mouth, skin, and gut [2-5]. With the advent of genome sequencing, numerous emerging studies have investigated the human microbiome for its unique diversity and metabolic processes and their direct impact on patient health. One of the largest reservoirs is the gut microbiome, which has been a target of recent investigation for its potential for manipulation. Next-generation sequencing technologies have enabled detailed 16S ribosomal RNA sequencing studies associating gut microbiome compositions with various pathologies spanning gastrointestinal and neurological disorders. However, establishing causation is challenging, and gnotobiotic animal models help explore these relationships [6].

An individual's microbiome composition and metabolism are not predetermined nor remain static throughout their lives; rather, several factors influence one’s gut microbiome. One’s genetics has been shown to

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have a considerable influence, with family members within the same household having nearly identical gut microbiomes [7-8]. Although genetics plays a role, the more dominant influences are external environmental factors [7-9]. These environmental factors can include diet, pharmaceutical use, amount and type of exercise, and metabolic measures such as obesity and glucose levels [9]. Due to this, the population of the human microbiome has the potential to be dynamic by altering these factors and influences. Alterations can occur within days, with the exact rate of change varying amongst individuals and being dynamic itself [9-11]. These changes have downstream effects on pathological and physiological processes, which can benefit the host or possibly be detrimental. Furthermore, these changes in the gut microbiome's population and, by extension, metabolic processes can affect numerous other body systems. Once such a system is the proposed "gut-brain axis": a complex, bi-directional pathway in which the gut microflora's composition and metabolic processes lead to influences of the central nervous system (CNS) and vice versa [5-6].

The gut-brain axis exists as a communication network between the CNS and gut microflora using neural, hormonal, and immune signaling and acts as the proposed bi-directional mechanism of the impact of anesthetics on the gut microbiome and vice-versa [6]. This relationship is increasingly recognized as profoundly impacting the gut and CNS functions. These influences may be caused by the gut's influence via the vagus nerve, leading to a direct, neurochemical connection to the CNS. It has also been shown that microbiota metabolism can produce neurotransmitters and metabolic precursors such as tryptophan, leading to the upregulation of specific biochemical pathways within the CNS [12-13]. Further connections exist with gut microbial-associated molecular patterns (MAMPS), such as lipoproteins, double-stranded RNA, lipopolysaccharides, and miRNA, leading to blood-brain-barrier (BBB) fortification, compromise, or triggering an immune response within the CNS [12,14-15]. However, dysfunction or disease within the CNS, or any organ system for that matter, is directly caused by the microbiome or microflora within the gut, but rather its association and impact upon these that can be a focus for potential iatrogenic manipulation. These are of obvious importance when discussing the practices of anesthesia and pain management via pharmaceutical impact.

Outpatient Surgeries and Spinal Anesthesia

Spinal anesthesia is a straightforward and dependable procedure with a success record of more than 90 percent. Because One of the most important considerations in deciding on the type of anesthetic to utilize is the ease with which the patient can recover postoperatively, controlling post - operative pain, vomiting and nausea, and urinary retention are all things to consider. These side effects might lead to a delay in hospital release or an unexpected return to the hospital [6].

Anesthetics and Opioids on Gut Microbiome

The current understanding of pharmaceutical introduction and microbiome influence and consequence is still at a baseline understanding. Numerous observations at an animal model level have shown a significant impact of opioid and anesthetic regimens, where even minimal intervention can potentially cause significant microbial changes [16]. Several species of mice gut flora, including Proteobacteria, Actinobacteria, Firmicutes, and Clostridiales, were altered several days after a 4-hour exposure to volatile anesthetics [16-17]. In a previous study, mice in all three groups who underwent anesthesia had significant alterations in their gut microbiome, seeing a decrease in a class of microbes from baseline prior to anesthesia exposure [18]. This study showed that the most significant decline was of Deferribacteres, whereas Fusobacteria and Proteobacteria were enriched after anesthesia exposure compared to the baseline [6,18]. Bacteroidales and Lachnospiraceae also significantly decreased post-anesthesia [6,18]. Further, nonvolatile anesthetics have been shown to impact gut microflora. Continuous 3-hour intravenous propofol decreased the abundance of Prevotella and Lactobacillus, which eventually recovered after >14 days [19]. These results suggest that, at least within an animal model, both volatile and nonvolatile anesthetic regimens have been shown to affect the composition of the gut microbiome; however, the impact on human models has yet to be determined.

It is common knowledge of the impact of opioid use on gut physiology. However, recent studies have illuminated a bi-directional impact of the gut microbiome affecting the metabolism and efficacy of opioids for the host [20]. It has been shown in mouse models that morphine administration immediately alters the host microbiome [20]. This alteration further changed the host serum concentrations of bile acids, phosphatidylethanolamines, and fatty acids via the microbiome, reversible through naltrexone administration [20]. Further, categorizing changes witnessed with morphine administration revealed that the composition of two bacterial groups, Bifidobacteria and Lactobacillaeae, were significantly depleted by opioid use and were associated with increased tolerance to opioids [21]. However, it was observed that germ-free mice and antibiotic-treated mice were less prone to developing opioid tolerance than were naïve mice [21]. It can, therefore, be inferred that not only can the gut microbiome be altered by opiate use, but that exact mechanism can alter the metabolism of the opiates

themselves. Of course, these preclinical studies must be first verified with clinical studies.

Pain and the Gut Microbiome

Many aspects of pain and microbiome populations have been historically heavily studied, with one of the most common complaints of irritable bowel syndrome (IBS) being heavily cataloged. As discussed earlier, the diversity of one's microbiome is highly personal to the individual and is influenced by multiple factors. Interestingly, when comparing the microbiome of those with an established diagnosis of IBS, these microbiomes are similar to each other, but also to healthy individuals bar a few subspecies of Bifidobacterium, Faecalibacterium, Faecalibacterium, Lactobacillaceae, Bacteroides, and Enterobacteriaceae [22]. This similarity was further explored when fecal transplantation from humans with microbiome signatures of IBS, as well as the phenotypic symptoms of constipation versus diarrhea, to healthy, germ-free mice developed gut-barrier dysfunction and anxiety [23]. These changes have caused several theories for explanation, including several metabolic pathway alterations leading to a decrease in short-chain fatty acids, changes in luminal bile acids, and failure of the purine salvage pathway [24].

When discussing systematic chronic pain syndromes, recent studies within the fibromyalgia literature have identified several ties with the gut microbiome [24-25]. One study highlights the ties between several species of gut microflora populations between fibromyalgia patients versus healthy individuals, with changes in P. merdae, P. copri, and A. muciniphila, and the degree of these changes reflected the severity of symptoms [24-25]. These microbiome composition changes were so profound that, when analyzed by a trained algorithm, a computer could classify fibromyalgia patients from healthy controls [25]. Changes in serum concentration of short-chain fatty acids, including butyrate and propionate, were also observed [25].

Recent studies have highlighted the significant role of the gut microbiome in developing neuropathic pain, revealing potential mechanisms [26]. One study found notable alterations in the gut microbiome composition in rats with chronic constriction injury to the sciatic nerve compared to sham-treated rats, with specific taxa correlating with clinical symptoms [26]. Changes in metabolites were also observed, with a decrease in butyrate-producing bacteria correlating with levels of β-hydroxybutyric acid [25]. Similar alterations were noted in humans with chronic pain conditions. Additionally, other studies demonstrated a causal role of the gut microbiome in neuropathic pain development, as evidenced by the prevention of mechanical hyperalgesia in antibiotic-treated or germ-free mice in a chemotherapy-induced neuropathic pain model [27]. This effect was associated with increased exposure of dorsal root ganglia to lipopolysaccharide, triggering an inflammatory response [27].

Increasing evidence supports the idea that the gut microbiome plays a causal role in murine neuropathic pain models, chemotherapy-induced neuropathic pain, and chronic pain syndromes. These underscore potential mechanisms linked to circulating bacterial metabolites and lipopolysaccharide levels, immune responses, and microglia activation. However, the clinical significance of these findings remains to be determined.

Future Directions

Given the qualities discussed thus far regarding the gut microbiome and the CNS, there lies a potential for iatrogenic manipulation within anesthesia and pain management. These theories and methods have the potential to help reduce harmful perioperative outcomes, postoperative pain, or postoperative neurocognitive impact while taking advantage of the next frontier in medicine by offering a personalized approach to the anesthetic care plan.

Artificial Intelligence

Artificial intelligence (AI) is a tool that can create more opportunities for researchers to create a catalog for individualized/personalized medicine. With the variability of the human gut microbiota, it can be potentially challenging for researchers to analyze numerous works to identify individual species and how or when they cause changes. The application of AI for microbial identification and analysis has recently led to a more rapid and reliable synthesis of results compared to conventional methods [28-29]. AI algorithms can analyze genomic data aiding clinicians and researchers in identifying the pathogens within the gut by recognizing patterns, predicting outcomes, and enhancing the efficiency of microbe analysis [28]. As this field continues to grow, an increasing number of microbial species are being identified, proving to cause changes in a patient's ability to tolerate certain medications and vice versa [6,16-17,19]. Artificial intelligence, and even machine learning, can be a convenient tool to increase the speed and accuracy of identifying specific changes [29].

AI is currently at the top of the Gartner Hype Cycle and as a result, there is an inflated number of expectations as to how AI might influence the anesthesia of choice over the next 10 to 50 years [30]. Understanding that most expectations may not come to fruition, one can perceive that this new tool, just as with the television or internet's effects on the fields of medicine, might provide a number of benefits such as increased efficiency and effective clinical care. When designed appropriately, AI can and is expected to improve clinical care by additionally

removing the extent of cognitive load on the physician, allowing for an overall higher quality of care.

The biggest and most likely outcome is that unlike humans, AI is able to quickly sort drugs into categories of those with and without interactions based on an individual's microbiome composition [29]. Second, AI has less errors than humans in regard to dosing when programmed appropriately [28-29]. Lastly, when AI is given genetic information, it would be able to incorporate that data into the selection of an appropriate set of drugs and doses that would enable the patient to receive appropriate medication doses [29]. The authorial team is aware of the limitations AI possesses and will not completely eradicate errors in the field, however, as was seen with the birth of electronic medical records, there can be an expected sharp decline in the number of near misses and potentially a decrease in the overall number of herald events, providing this new field with additional benefits to couple with the novel ideas presented in this paper [29]. The use of AI can be leveraged to potentially create a catalog of different gut microbial patterns and individualized changes seen in certain patients, predict the best course of action, identify changes in the field as it relates to patients, create personalized medicine treatments, and so much more [31]. This AI-created catalog could help future clinicians and researchers explicitly map out what microbiome species impact anesthesia and vice versa.

Microbiome composition testing

Collecting pre- and post-anesthesia stool samples should be critical to any research on the topic. Stool samples provide clinicians with many options for assessing the gut microbiome composition [32]. Standard tools for making these assessments include a traditional culture, qPCR, 16S sequencing, and computationally heavy MGS [32]. As research in the human gut microbiome grows, these available modern diagnostic technologies have facilitated significant advancements in knowledge. Each exhibits unique capabilities that provide clinicians insight into the micro-communities that make up one's gut [32]. These tools have been and continue to be a standard when compiling research data on the gut microbiome. They should be used for the research being presented in this paper as it creates the best means to assess the relationship between anesthetic drugs and the intestinal microflora.

Stool samples are necessary for this research as complete stool samples can give a clear window into the gut microbiota and the changes at specific points and over time in anesthesia care [33]. Optimizing the collection, processing, storage, and preservation of samples is essential for biomarker, microbe, and pattern discovery [33].

Interventional microbiome alterations

In understanding the role which anesthetics can play in altering the gut microbiome, a preemptive approach can be taken in patients by providing interventional microbiome alterations in hopes of improved outcomes. The literature clearly states that exposure to anesthetic agents can significantly alter the diversity of gut microflora [6]. Thus, clinicians can utilize this information to better serve their patients by altering their gut microbiota when needed [6]. In addition to understanding this relationship to improve patients' gut health and post-surgery GI recovery, research on this topic can help clinicians better understand the harmful effects of altering the gut microbiome on anesthesia action [6].

Though there is only preliminary research showing promising data, it has been noted that early evidence suggests the gut microbiome is associated with sensitivity to certain anesthetics [6]. One study showed that when specific pathogen-free and germ-free mice were exposed to pentobarbital anesthesia, the germ-free mice displayed a much faster recovery than the specific pathogen-free mice [6,34]. As discussed previously, the gut microbiome may affect the response to certain medications for pain, such as opioids, as the interactions between these medications' receptors and the microbiome are bidirectional [6].

The study presented data that suggested that the administration of morphine can result in significant changes in the composition of the gut microbiome [6,35]. As the receptors are bi-directional, the pre-opioid gut microbiome composition can affect the host response and metabolism of the opioid [6,35].

These studies are prime examples of why this topic needs further evaluation. Medicine is on the cusp of better understanding how to make anesthetic and pain management drugs more effective and how to protect patients' gut microbiome composition pre- and post-anesthetic exposure more adequately.

By using this knowledge and understanding of these relationships, clinicians will have an entire already-existing arsenal to better treat their patients by providing interventional microbiome alterations. Currently used in standard practice, many methods include diet modifications, pre/probiotics, fecal transplantation, and microbial enzyme inhibitors [36]. These methods can continue to be used to potentially allow patients to tolerate anesthetic procedures better, reduce opioid effects, shorten surgical recovery time, aid in longer duration of opioid effects, and more as needed. Research on these relationships should be further explored as it can benefit clinicians and their future patients in many scenarios.

Conclusion

Using the microbiome as the missing part of the current patient assessment for surgical intervention is likely the new direction for precision medicine, especially as clinicians look forward to continual progress with tools such as artificial intelligence. In understanding the parts and the synergistic effects of the different flora species within the microbiome, clinicians will be able to make better decisions regarding the needs of the patients and, as mentioned above, take action to better intervene on their behalf in this critical moment both for surgical sedation and in the pain management clinics. These subsequent changes are the small steps needed for the giant leaps in better patient care.

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