The gut microbiome and postoperative pain

Authors

Ilaria Converti[1*]

1 Division of Plastic and Reconstructive Surgery, Mater Dei Hospital, Bari, Italy

Corresponding author

Ilaria Converti
Division of Plastic and Reconstructive Surgery
Mater Dei Hospital, 70121 Bari, Italy
Email: ilaria.converti@gmail.com

ABSTRACT

Despite recognition of the prevalence of postoperative pain, and improvements in pain management techniques, poorly controlled postoperative pain remains a major unresolved challenge globally. Traditional analgesics and interventions are often ineffective or partially effective in the treatment of postoperative pain, resulting in a chronic pain condition with related socio-economic impacts and reduced quality of life for the patient. The relationship between gut microbiota and neurological diseases, including chronic pain, has received increasing attention. The gut microbiome is a crucial modulator of visceral pain, whereas recent evidence suggests that gut microbiota may also play a critical role in many other types of chronic pain, including inflammatory pain, headache and neuropathic pain.

Keywords: anesthesia, drugs, gut microbiome, postoperative pain.

TEXT

Despite recognition of the prevalence of postoperative pain, and improvements in pain management techniques, poorly controlled postoperative pain remains a major unresolved challenge globally. An estimated 71% and 51% of patients experience moderate to severe pain after surgery in in-patient and outpatient settings, respectively. Inadequately controlled pain after surgery is associated with significant perioperative morbidity including myocardial infarction and pulmonary complications.[1-6] The most common triggers of somatic pain are traumatic injuries and surgery. Extensive research has been conducted over decades into the nature and characteristics of surgical pain. Pre-clinical studies have been an important element of this research. Early animal models of incisional pain and plantar incision in rodents representing surgical trauma, did not completely represent the complex pathophysiology of surgical pain.[1,7,8] Traditional analgesics and interventions are often ineffective or partially effective in the treatment of postoperative pain, resulting in a chronic pain condition with related socio-economic impacts and reduced quality of life for the patient. Such chronic pain which occurs after surgery is referred to as Persistent Post-Surgical Pain.[1,9-12] The complex ecosystem that is the gastrointestinal microbiota plays essential roles in the maintenance of the healthy state of the host. A disruption to the balance of this microbiome has been implicated not only in gastrointestinal disease but also neurological disorders including chronic pain. The influence of the gut microbiome is well documented in the context of visceral pain from the gastrointestinal tract while a greater understanding is

emerging of the impact on inflammatory pain and neuropathic pain.[1,13,14] The gut microbiome is an essential source for driving immune maturation and maintaining appropriate immune response. Given that inflammatory processes have been implicated in postoperative pain, aberrant microbiome profiles may play a role in the development of this type of pain. Furthermore, the microorganisms in our gut produce metabolites, neurotransmitters, and neuromodulators which interact with their receptors to regulate peripheral and central sensitization associated with chronic pain.[1,24,25] Microbiota-derived mediators can also regulate neuroinflammation, which is associated with activation of microglia as well as infiltration by immune cells, known to modulate the development and maintenance of central sensitization. Moreover, risk factors for developing postoperative pain include anxiety, depression, and increased stress response.[1,15,18] The relationship between gut microbiota and neurological diseases, including chronic pain, has received increasing attention. The gut microbiome is a crucial modulator of visceral pain, whereas recent evidence suggests that gut microbiota may also play a critical role in many other types of chronic pain, including inflammatory pain, headache, neuropathic pain, and opioid tolerance.[19-22] Numerous signaling molecules derived from gut microbiota, such as by-products of microbiota, metabolites, neurotransmitters, and neuromodulators, act on their receptors and remarkably regulate the peripheral and central sensitization, which in turn mediate the development of chronic pain.[19,23-25] Gut microbiota-derived mediators serve as critical modulators for the induction of peripheral sensitization, directly or indirectly regulating the excitability of primary nociceptive neurons. In the central nervous system, gut microbiota-derived mediators may regulate neuroinflammation, which involves the activation of cells in the blood-brain barrier, microglia, and infiltrating immune cells, to modulate induction and maintenance of central sensitization.[19,26-30] Neuropathic pain is also induced by peripheral nerve trauma which can be studied in the pre-clinical setting using the rat model of spared nerve injury. Using this model, it was noted that an altered gut microbiota composition was associated with anhedonia behavior in susceptible compared to sham-operated rats or resilient rats.[1] Neuropathic pain can develop after nerve injury, when deleterious changes occur in injured neurons and along nociceptive and descending modulatory pathways in the central nervous system.[31,32] The myriad neurotransmitters and other substances involved in the development and maintenance of neuropathic pain also play a part in other neurobiological disorders. This might partly explain the high comorbidity rates for chronic pain, sleep disorders, and psychological conditions such as depression, and why drugs that are effective for one condition may benefit others.[31] Neuropathic pain can be distinguished from non-neuropathic pain by two factors.[31,33] Firstly, in neuropathic pain there is no transduction. Secondly, the prognosis is worse: injury to major nerves is more likely than injury to non-nervous tissue to result in chronic pain. In addition, neuropathic pain tends to be more refractory than non-neuropathic pain to conventional analgesics, such as non-steroidal anti-inflammatory drugs and opioids. Investigations are needed to determine the specific role of the gut microbiome in this type of pain which may help inform the development of preventative interventions as well as management strategies to improve patient outcome.[1,34-40] Therefore, further studies to evaluate the relationship between the gut microbiome, brain axis and pain are needed.

REFERENCES

[1] Brenner D, Shorten GD, O'Mahony SM. Postoperative pain and the gut microbiome. Neurobiol Pain. 2021;10:100070.

[2] Corsalini M, Di Venere D, Carossa M, et al. Comparative clinical study between zirconium-ceramic and metal-ceramic fixed rehabilitations. Oral Implantology 2018;11(3):150–160.

[3] Di Naro E, Loverro M, Converti I, et al. The

Effect of Menopause Hypoestrogenism on Osteogenic Differentiation of Periodontal Ligament Cells (PDLC) and Stem Cells (PDLCs): A Systematic Review. Healthcare (Basel) 2021;9(5):572.

[4] Rapone B, Converti I, Santacroce L, et al. Impact of Periodontal Inflammation on Nutrition and Inflammation Markers in Hemodialysis Patients. Antibiotics 2019;8(4):209.

[5] Lizana J, Reinoso CMD, Aliaga N, et al. Bilateral central retinal artery occlusion: An exceptional complication after frontal parasagittal meningioma resection. Surg Neurol Int. 2021;12:397.

[6] Rapone B, Pedone S, Carnevale A, et al. Profilometer Comparison of the Surface Roughness of Four Denture Base Resins: An In Vitro Study. Applied Sciences. 2022;12(4):1837.

[7] Brennan TJ, Vandermeulen EP, Gebhart GF. Characterization of a rat model of incisional pain. Pain. 1996;64(3):493-502.

[8] Rapone B, Ferrara E, Montemurro N, et al. Oral microbiome and preterm birth: correlation or coincidence? A narrative review. Open Access Macedonian Journal of Medical Sciences 2020;8(F):123-132.

[9] Femiano F, Gombos F, Scully C. Recurrent aphthous stomatitis unresponsive to topical corticosteroids: A study of the comparative therapeutic effects of systemic prednisone and systemic sulodexide. Int J Dermat 2003;42(5):394-7.

[10] Rapone B, Ferrara E, Santacroce L, et al. Gingival crevicular blood as a potential screening tool: a cross sectional comparative study. Int. J. Environ. Res. Public Health 2020;17(20):7356.

[11] Corsalini M, Rapone B, Cagnetta G, et al. Orofacial functions and chewing effiency in elderly patients with Parkinsons's disease rehabilitated with removable prostheses. The Open Dentistry 2020;14:13-18.

[12] Rapone B, Ferrara E, Qorri E, et al. The Impact of Periodontal Inflammation on Endothelial Function Assessed by Circulating Levels of Asymmetric Dimethylarginine: A Single-Blinded Randomized Clinical Trial. Journal of Clinical Medicine. 2022;11(14):4173.

[13] Di Venere D, Rapone B, Corsalini M. Dental trauma in the anterior sector: an analysis of the predisposing factors in a group of orthodontic patients. Clinica Terapeutica 2020;171(6):e481-485.

[14] Rapone B, Inchingolo AD, Trasarti S, et al. Long-Term Outcomes of Implants Placed in Maxillary Sinus Floor Augmentation with Porous Fluorohydroxyapatite (Algipore®FRIOS®) in Comparison with Anorganic Bovine Bone (Bio-Oss®) and Platelet Rich Plasma (PRP): A Retrospective Study. J Clin Med. 2022;11(9):2491.

[15] Rapone B, Ferrara E, Santacroce L, et al. Periodontal Microbiological Status Influences the Occurrence of Cyclosporine□A and Tacrolimus□ Induced Gingival Overgrowth. Antibiotics 2019;8(3):124.

[16] Montemurro N, Condino S, Cattari N, et al. Augmented Reality-Assisted Craniotomy for Parasagittal and Convexity En Plaque Meningiomas and Custom-Made Cranio-Plasty: A Preliminary Laboratory Report. Int J Environ Res Public Health. 2021;18(19):9955.

[17] Rapone B, Ferrara E, Santacroce L, et al. The Gaseous Ozone Therapy as a Promising Antiseptic Adjuvant of Periodontal Treatment: A Randomized Controlled Clinical Trial. Int J Environ Res Public Health. 2022;19(2):985.

[18] Lizana J, Montemurro N, Aliaga N, et al. From textbook to patient: a practical guide to train the end-to-side microvascular anastomosis. Br J Neurosurg. 2021;7:1-5.

[19] Guo R, Chen LH, Xing C, Liu T. Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. Br J Anaesth. 2019;123(5):637-654.

[20] Lorusso F, Postiglione F, Delvecchio M, et al. The impact of diabetes on implant oral

rehabilitations: a bibliometric study and literature review. Acta Medica Mediterranea 2020;36:3333.

[21] Rapone B, Palmisano C, Ferrara E, et al. The Accuracy of Three Intraoral Scanners in the Oral Environment with and without Saliva: A Comparative Study. Appl. Sci. 2020;10(21):7762.

[22] Montemurro N. Telemedicine: Could it represent a new problem for spine surgeons to solve? Global Spine J. 2022;12(6):1306-1307.

[23] Corsalini M, Di Venere D, Sportelli P, et al. Evaluation of prosthetic quality and masticatory efficiency in patients with total removable prosthesis: study of 12 cases. Oral Implantology 2018;11(4):230–240.

[24] Chavda V, Chaurasia B, Fiorindi A, et al. Ischemic Stroke and SARS-CoV-2 Infection: The Bidirectional Pathology and Risk Morbidities. Neurol Int. 2022;14(2):391-405.

[25] Vaccaro AR, Lambrechts MJ, Karamian BA, et al. Global Validation of the AO Spine Upper Cervical Injury Classification. Spine (Phila Pa 1976). 2022 Jul 25.

[26] Lambrechts MJ, Schroeder GD, Karamian BA, et al. Effect of surgical experience and spine subspecialty on the reliability of the AO Spine Upper Cervical Injury Classification System. J Neurosurg Spine. 2022;19:1-11.

[27] Guo R, Chen LH, Xing C, Liu T. Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential. Br J Anaesth. 2019;123(5):637-654.

[28] Scarola R, Montemurro N, Ferrara E, Corsalini M, Converti I, Rapone B. Temporomandibular Disorders and Fibromyalgia: A Narrative Review. Open Access Maced J Med Sci 2021;9(F):106-12.

[29] Gaeta G, Gombos F, Femiano F, et al. Acitretin and treatment of the oral leucoplakias. A model to have an active molecules release. J Eur Academy Dermat Venereology 2000;14(6):473-8.

[30] Femiano, F., Scully, C. Functions of the cytokines in relation oral lichen planus-hepatitis C. Med Oral, Patol Oral, Cir Buccal 2005;10(1).

[31] Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. BMJ. 2014, 348:f7656.

[32] Ahsan K, Khan SI, Zaman N, et al. Fusion versus nonfusion treatment for recurrent lumbar disc herniation. J Craniovertebr Junction Spine. 2021;12(1):44-53.

[33] Mishra R, Deora H, Florez-Perdomo WA, et al. Clinical and Radiological Characteristics for Recurrence of Chronic Subdural Hematoma: A Systematic Review and Meta-Analysis. Neurol Int. 2022;26;14(3):683-695.

[34] Perinetti G, D'Apuzzo F, Contardo L, et al. Gingival crevicular fluid alkaline phosphate activity during the retention phase of maxillary expansion in prepubertal subjects: A split-mouth longitudinal study. Am J Orthod Dentofacial Orthop 2015;148(1):90-6.

[35] Dang QT, Huynh TD, Inchingolo F, et al. Human Chondrocytes from Human Adipose Tissue-Derived Mesenchymal Stem Cells Seeded on a Dermal-Derived Collagen Matrix Sheet: Our Preliminary Results for a Ready to Go Biotechnological Cartilage Graft in Clinical Practice. Stem Cells Int. 2021;2021:6664697.

[36] Lei L, Ji M, Yang J, Chen S, et al. Gut microbiota-mediated metabolic restructuring aggravates emotional deficits after anesthesia/surgery in rats with preoperative stress. Front Immunol. 2022;13:819289.

[37] Li Z, Sun T, He Z, Li Z, et al. SCFAs Ameliorate Chronic Postsurgical Pain-Related Cognition Dysfunction via the ACSS2-HDAC2 Axis in Rats. Mol Neurobiol. 2022;59(10):6211-6227.

[38] Zhang Z, Shi F, She J. Robot-assisted tumorectomy for an unusual pelvic retroperitoneal leiomyoma: A case report. Medicine (Baltimore). 2022;101(31):e29650.

[39] Minerbi A, Shen S. Gut Microbiome in An-

esthesiology and Pain Medicine. Anesthesiology. 2022;137(1):93-108.

[40] Wang EJ, Cohen SP. Chronic Postoperative Pain and Microorganisms: The Good, the Bad, and the Ugly. Anesth Analg. 2022;134(4):696-698.