Electrical stimulation as a promising therapeutic in inflammatory bowel disease: a scoping review / estimulação

Elétrica como terapêutica promissora na doença inflamatória intestinal: uma revisão de escopo

DOI:10.34117/bjdv8n8-038

Recebimento dos originais: 21/06/2022
Aceitação para publicação: 29/07/2022

Jefferson Ícaro Soares
Graduado em Enfermagem pela Escola de Enfermagem de Ribeirão Preto da Universidade de São Paulo (EERP - USP)
Institution: Universidade de São Paulo (EERP - USP)
Address: Avenida Bandeirantes, 3900, Campus Universitário, CEP: 14040-902, Ribeirão Preto - SP, Brasil
E-mail: jefferson.icaro@usp.br

Adriana Barbosa Ribeiro
Pós-doutoranda pela Faculdade de Odontologia de Ribeirão Preto da Universidade de São Paulo (USP)
Institution: Universidade de São Paulo (USP)
Address: Avenida do Café, s/n, Campus Universitário, CEP: 14040-904, Ribeirão Preto - SP, Brasil
E-mail: driribeiro@usp.br

Ulisses Ávila Reis
Graduando em Medicina pelo Centro Universitário Barão de Mauá
Institution: Centro Universitário Barão de Mauá
Address: Rua Ramos de Azevedo, 423, Jardim Paulista, CEP: 14090-180, Ribeirão Preto - SP, Brasil
E-mail: ui.lis@hotmail.com

Luiz Felipe Moreira Roque
Graduando em Medicina pelo Centro Universitário Barão de Mauá
Institution: Centro Universitário Barão de Mauá
Address: Rua Ramos de Azevedo, 423, Jardim Paulista, CEP: 14090-180, Ribeirão Preto - SP, Brasil
E-mail: luizfelipemoreiraroque@gmail.com

Helio Cesar Salgado
Doutor pela Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FMRP)
Institution: Universidade de São Paulo (FMRP)
Address: Avenida Bandeirantes, 3900, Campus Universitário, CEP: 14040-900, Ribeirão Preto - SP, Brasil
E-mail: hcsalgado@fmrp.usp.br

Aline Barbosa Ribeiro
Doutora pelo Centro Universitário Barão de Mauá
Institution: Centro Universitário Barão de Mauá
Address: Rua Ramos de Azevedo, 423, Jardim Paulista, CEP: 14090-180, Ribeirão Preto - SP, Brasil
E-mail: aline.barbosa@baraodemaua.br

ABSTRACT
The central nervous system has extensive innervation spread to the gastrointestinal tract, providing the possibility for using nerve stimulation to treat gastrointestinal diseases, such as Inflammatory Bowel Disease (IBD). This review aimed to carry out a bibliographic survey of the primary clinical studies that correlate IBD treatment with neural electrical stimulation. The following databases were consulted: PubMed, Embase, Cochrane, and BioMed. A total of 477 articles were screened at the titles and abstract level, of which 210 were also assessed at the full text for eligibility. The eleven articles identified for inclusion were selected in this review. The search terms used for the search included: "electrical stimulation", "electrical neuromodulation", "inflammatory bowel disease", "ulcerative colitis", and "Crohn's Disease". The nerves modulate inflammation in the gut, however, the clinical protocols for anti-inflammatory effects have had variable success. There is still little scientific evidence for an accurate clinical decision for using this electroceutical approach. Therefore, further studies are needed to reduce the heterogeneity of clinical protocols.

Keywords: inflammatory bowel disease, crohn's disease, ulcerative colitis, electrical stimulation, neuromodulation.

RESUMO
O sistema nervoso central tem extensa inervação do trato gastrointestinal, proporcionando a possibilidade de usar a estimulação nervosa para tratar doenças gastrointestinais, como a Doença Inflamatória do Colón (DII). Esta revisão teve como objetivo realizar um levantamento bibliográfico dos estudos clínicos primários que correlacionam o tratamento da DII com a estimulação elétrica neural. Foram consultados os seguintes bancos de dados: PubMed, Embase, Cochrane, e BioMed. Um total de 477 artigos foram analisados em nível de título e resumo, dos quais 210 também foram avaliados no texto completo para elegibilidade. Os onze artigos identificados para inclusão foram selecionados nesta revisão. Os termos de busca utilizados para a pesquisa foram incluídos: "estimulação elétrica", "neuromodulação elétrica", "doença inflamatória intestinal", "colite ulcerativa", e "doença de Crohn". Os nervos modulam a inflamação no intestino, entretanto, os protocolos clínicos para efeitos anti-inflamatórios tiveram sucesso variável. Ainda há poucas evidências científicas para uma decisão clínica precisa para o uso desta abordagem eletromacêutica. Portanto, são necessários mais estudos para reduzir a heterogeneidade dos protocolos clínicos.

Palavras-chave: doença inflamatória intestinal, doença de crohn, colite ulcerativa, estimulação elétrica, neuromodulação.

1 INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition whose prevalence has increased substantially worldwide [1]. In particular, IBD has been a challenge for public health since this disease affects mainly the population aged 30-60 years [2]. Nevertheless, IBD does not have a favourable prognosis because it does not have a conspicuous clinical treatment since remission periods followed by recurrences mark it. The primary forms of IBD are Crohn's Disease and Ulcerative Colitis [3]. Crohn's Disease can involve the whole digestive tract (from mouth to the anus), while Ulcerative Colitis can compromise the recto-colon only.

Although the etiology of IBD is still not completely understood, this morbidity is suggested to occur due to complex interactions between host genetics, dysbiosis of the intestinal microbial flora, and environmental factors [4]. These factors trigger an inappropriate release of pro-inflammatory cytokines, characterized by changes in the intestinal mucosa and the immune system, compromising structurally and functionally the intestinal epithelium [5]. Accumulating evidence suggests that controlling the inflammatory response is essential in the early treatment of IBD [6].

Current treatments for inducing remission of IBD include immunomodulatory agents; however, the value in promoting cure is unclear and controversial, especially considering individual patient variations [7]. In addition, IBD patients report noncompliance, side effects to medications, and refractoriness to the therapeutic approach [8]. Recent studies showed that innovative therapies based on nerves or brain centre’s electrical stimulation were powerful medicines for treating inflammatory diseases, such as IBD [9]. Studies have shown that the gastrointestinal tract has a two-way neural interaction with the central nervous system through the vagus nerve, thoracolumbar connections, and sacral nerves, which provide the electrical neuromodulator's therapeutic effect of IBD [9]. On top of that, it has been demonstrated that vagus nerve stimulation controls inflammation by a cholinergic anti-inflammatory pathway in preclinical and clinical studies [10-12].

In the present review, detailed information is provided regarding a clinical basis for electrical stimulation of different nerves on IBD remission. Moreover, this review focuses on vagus nerve stimulation's anti-inflammatory properties as a potential therapy for IBD. Subsequently, current knowledge about the possible mechanisms and reasons for failures or limited success and how treatments might improve IBD.

2 MATERIALS AND METHODS

This study is based on a bibliographic survey concerning the electroceutical treatment for IBD. This article followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A literature search of PubMed, Embase, Cochrane, and BioMed Central was performed in order to identify scientific articles published in English up to January 2021. The keywords and Boolean operators used for the search included: "electrical stimulation" OR "electrical neuromodulation"; AND "inflammatory bowel disease" OR "ulcerative colitis" OR "Crohn's disease." The detailed search strategy is provided in Figure 1.

The selection process considered the following criteria:

Inclusion:

a) articles that addressed the theme of the bibliographic review

b) articles that presented the descriptors

c) clinical articles

d) articles associated with treatments with electrical stimulation of IBD

Exclusion Criteria:

a) duplicate articles

b) articles with titles that did not include the descriptors

c) articles from experimental essays and bibliographic reviews

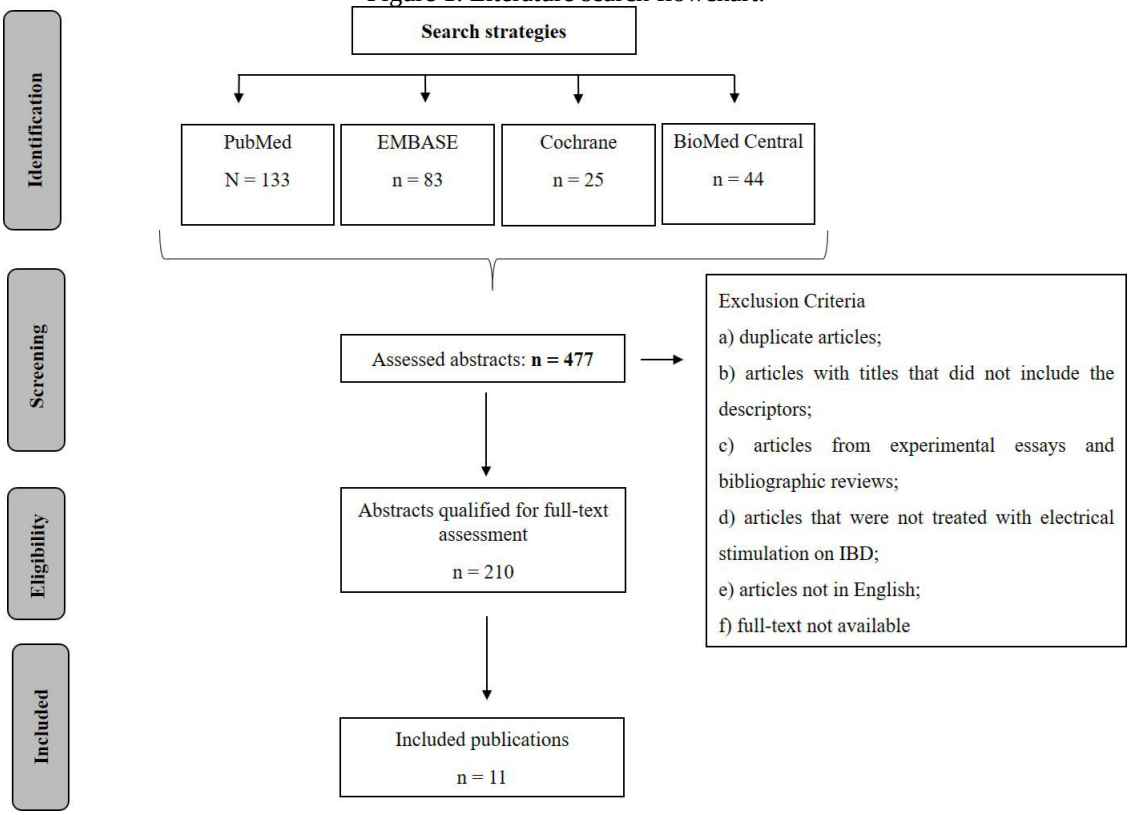
d) articles that were not treated with electrical stimulation on IBD

e) articles not in English

f) full-text not available.

After a search based on the established exclusion and inclusion criteria, 477 articles were found. In the first analysis, 267 articles were excluded because the title was not related to the study's aim, while their abstracts excluded 201 articles. Thus, the reading of 11 selected articles was performed for this review. Because few clinical studies have investigated an electroceutical approach in patients with IBD, the review concentrated on identifying the highest evidence levels.

Figure 1. Literature search flowchart.



3 DISCUSSION

3.1 GASTROINTESTINAL TRACT INNERVATION

The digestive system is innervated by connecting with the central nervous system by vagal, sacral, and thoracolumbar nerves. Moreover, the gastrointestinal tract is also innervated by the enteric nervous system, which concerts with central nervous system reflexes and command centres, and neural pathways. For this reason, there is a bidirectional flow of information between the central nervous system and the enteric nervous system. Of note, the enteric nervous system in humans contains 200-600 million neurons, distributed in small ganglia distributed into two plexuses: the myenteric (from the upper esophagus to the internal anal sphincter) and submucosa (small and large intestines) [13]. In addition, sensory neurons release many mediators from their peripheral endings by efferent function. This function carries information about the gastrointestinal tract, including intrinsic contents, physical state, and homeostasis alteration such as inflammation. The vagus, thoracolumbar and sacral nerves have a potential disease-modifying role, targeted through electrical stimulation therapy, to modify some pathological conditions such as IBD through implanted electrodes and electrical current application [TABLE 1].

3.2 IBD

The intestinal epithelium is composed of a protective barrier that separates the intestinal lumen's interior and concentrates a large bacterial population from the sterile internal environment [14]. This epithelial barrier is formed by cellular structures that provide the immune system's mechanical protection and defense cells, constituting a functional immune barrier. The intestinal epithelial barrier prevents bacterial agents and other toxins in the intestinal lumen from migrating into the internal environment, causing bacteremia and septicemia [14]. Nowadays, it is admitted that the inflammatory process in the intestinal barrier in patients with inflammatory bowel diseases begins with the breakdown of this epithelial defense system.

IBD has a little-known etiology, but studies provide new data on the pathogenesis of this intestinal inflammation. Due to complex interactions between host genetics, dysbiosis of intestinal microbiota, and environmental factors [4]. These factors induce sustained inflammation, characterized by an alteration in the intestinal mucosa and immune system [5]. Nevertheless, normal mucosal immune homeostasis disruption can exacerbate uncontrolled chronic inflammation, such as observed in Crohn's Disease and Ulcerative Colitis [15].

Cytokines play an essential role in the inflammatory process. They are responsible for influencing the activity, differentiation, proliferation, and survival of an immune cell and increase, or attenuate, the inflammatory response [14]. Studies have shown that TNF is a critical pro-inflammatory cytokine. For this reason, many treatments have used anti-TNF therapies for IBD treatment, but there is a 20-30% primary non-response rate [16]. Another alternative treatment is surgery in order to complications of IBD, such as perforation, abscess, and stenosis. However, the IBD can recur after the surgery. A treatment targeting the anti-inflammatory properties, as a non-drug therapy, could be used as an alternative therapy, such as electrical stimulation of the different nerves. In fact, electrical stimulation relies on the nervous system's neuromodulation, improving chronic diseases with fewer adverse effects than drugs [17].

Table 1: Clinical studies of electrical stimulations for IBD remission.

Reference	Electrical Stimulation	Stimulation Parameter	Outcomes
Clarençon et al., 2014 **(21)**	Vagus nerve stimulation	30 s ON e 5 min OFF, 500 ms, 10 Hz. 0.5–1.25 mA	Increase in parasympathetic tone, followed by clinical improvement with Crohn's disease remission.
Kibleur et al., 2018 **(22)**	Vagus nerve stimulation	30 s ON e 5 min OFF, 500 ms, 10 Hz. 0.5–1.25 mA	Normalization of bowel mucosal inflammation, anxiety state and vagal tone.
Bonaz et al., 2016 **(23)**	Vagus nerve stimulation	30 s ON e 5 min OFF, 500 ms, 10 Hz. 0.5–1.25 mA	Induced the IBD remission follow-up 6 months and increase in parasympathetic tone.
Bhatti et al., 2020 **(24)**	Gastrointestinal electrical stimulation	Not disclosed	Gastrointestinal symptoms and Crohn's symptoms significantly improved.
Sinniger et al., 2020 **(25)**	Vagus nerve stimulation	30 s ON e 5 min OFF, 500 ms, 10 Hz. 0.25 mA	Five patients were clinical IBD remission and six in endoscopic IBD remission. Increase in parasympathetic tone.
Holzer et al., 2008 **(33)**	Sacral Nerve Stimulation	210 μs, 20 Hz, 1.5 to 8.5 V (median, 5 V)	Seven patients reported amarked reduction of episodes of incontinence.
Brégeon et al., 2015 **(34)**	Sacral Nerve Stimulation	200 ms, 14 Hz, 0.5 to 1.5 V	Decrease in fecal incontinence and disease activity scores.
Vitton et al., 2008 **(35)**	Sacral Nerve Stimulation	5 Hz, 0.1 ms	Continence and quality of life were improved in all treated patients.
Kemler et al., 1999 **(38)**	Spinal Cord Stimulation	210 ms, 85 pulses/s, 1–2 V	After removal of the system, remission returned and remained.
Vitton et al., 2009 **(39)**	Transcutaneous Posterior Tibial Nerve Stimulation	200 μs, 10 Hz, 10 –30 mA	5 patients reported a significant symptomatic and quality of life improvement.
Neeb et al., 2019 **(40)**	Transcranial direct current stimulation	Not disclosed	Pain reduction associated with changes in resting-state functional in magnetic resonance imaging.

3.3 VAGAL NERVES STIMULATION ON IBD

The autonomic nervous system has two main branches based on function and anatomy: the sympathetic and parasympathetic arms. The sympathetic neurons begin in the thoracic and lumbar regions of the spinal cord, while the ganglia are located along a chain parallel to the spinal cord. However, the parasympathetic neurons arise in the brainstem and the lower sacral portion of the spinal cord, while the peripheral ganglia are located close to the organ. They innervate or within the organ itself [9]. The parasympathetic and sympathetic branches play an essential role in maintaining homeostasis when facing internal and external stressing factors, including severe

infections [18]. Also, they act by regulating the cardiac output, vascular tone, breathing control, airway resistance, regulation of the inflammatory response, adaptive immune modulation, gastrointestinal motility, and thermoregulation [18]. While humoral and cellular modulations may take hours, or days, to take effect, it is well known that the autonomic nervous system plays a significant role in the immune response during the initial phase of severe infection, with an instantaneous effect through the innate immune response [18]. The autonomic control provides opportunities for implementing electrical nerve stimulation for intestinal diseases.

On the top, an imbalance of the autonomic nervous has been reported in patients with IBD. Patients with Crohn's Disease showed sympathetic dysfunction [19]. In contrast, patients with Ulcerative Colitis exhibited vagal dysfunction [20]. Then, the chronic inflammation in IBD extends the spectrum of extraintestinal alterations to the nervous system. Moreover, dysautonomia in IBD may be related to psychological adjustment and pro-inflammatory exacerbation [19, 20]. Clarençon et al. (2014) showed a case report of long-term low-frequency vagus nerve stimulation in one patient with Crohn's Disease [21]. The patient presented a significant increase in parasympathetic tone, followed by clinical improvement with Crohn's Disease remission after 12 months [21]. Also, the patient showed significant clinical improvement with a reduced clinical disease index and reduced inflammation. Using low frequency vagus nerve stimulation, Kibleur et al. (2018) collected recorded electroencephalograms from nine patients with Crohn's Disease after six weeks and 12 months [22]. After six weeks, vagus nerve stimulation elicited an increased spectral power in delta and theta bands on frontal, temporal, and occipital areas. In addition, after 12 months, the chronic effect of vagus nerve stimulation decreased the power in the alpha frequency band, which was correlated with the normalization of the bowel mucosal inflammation, anxiety state, and vagal tone [22]. This study's main finding was the significant effect of vagus nerve stimulation in patients with Crohn's Disease.

The anti-inflammatory effects of vagal nerve stimulation have been well documented in pre-clinical studies [10]. In contrast, clinical trials, and case reports of vagal nerve stimulation for IBD remission have shown variable outcomes. In a small pilot study, chronic vagus nerve stimulation in seven patients presenting active Crohn's Disease induced IBD remission after six months [23]. Two patients with severe diseases left the study owing to worsening symptoms. The IBD remission was evaluated by biological (C-reactive protein and/or fecal calprotectin) and endoscopic parameters from five patients.

Also, the vagal nerve stimulation restored the vagal tone [23]. This study showed potential evidence for the electroceutical approach to the IBD treatment. Similar results were observed in a study that evaluated gastrointestinal electrical stimulation in eleven patients with Crohn's Disease with coexisting symptoms of gastroparesis [24].

Sinniger et al. (2020) described the outcomes of a pilot study conducted on nine patients with Crohn's Disease, continuously stimulated with an electrode wrapped around the cervical vagus nerve over one year [25]. Five patients exhibited clinical IBD remission and six endoscopic IBD remission after one year. Moreover, C-reactive protein, fecal calprotectin, and digestive pain scores decreased. Almost 35% of patients with IBD present chronic abdominal pain [26], which explains these results' relevance. In addition, seven patients restored their vagal tone, and the cytokines profile was close to normal [25]. More randomized studies with a higher number of patients are necessary to better characterize the vagal nerve stimulation on IBD remission and human Ulcerative Colitis.

3.4 INFLUENCE OF VAGAL NERVES ON GUT INFLAMMATION

Over the past twenty years, many studies aimed to assess the autonomic nervous system's role in modulating systemic inflammatory responses to many stressors [27]. The vagus nerve's role in modulating the body's immune responses has been significantly prominent. Studies have demonstrated that the vagus nerve's electrical stimulation induces an anti-inflammatory response in the gastrointestinal tract through interactions with the enteric nervous system [27]. Stimulating vagal afferents induces systemic anti-inflammatory responses mediated by the hypothalamus-pituitary-adrenal axis by releasing glucocorticoids from adrenal glands. The vagus's efferent (parasympathetic) activity also has a marked anti-inflammatory effect, characterizing the Inflammatory Reflex [28]. In fact, the release of acetylcholine at the end of its efferent fibers can inhibit the release of tumor necrosis factor-alpha via an interneuron of the enteric nervous system by macrophages [28].

This reflex's activation leads afferent (sensitive) information through the vagus to nuclei of the brain stem that control the efferent neural signals (motors) also transmitted by the vagus to the periphery [29-31]. The Inflammatory Reflex targets the spleen and other cytokine-producing organs, such as the intestine. The electrical vagus stimulation activates acetylcholine release from the celiac mesenteric ganglia, leading to stimulation of adrenergic neurons from the splenic nerve, communicating directly with T cells in the spleen. T cells' activation releases acetylcholine that binds to α-7 nicotinic acetylcholine

receptors (α-7nAChRs) on macrophages, resulting in the suppressing of pro-inflammatory cytokines explaining the IBD remission [28, 30, 31].

3.5 EFFECT OF SACRAL NERVES STIMULATION ON IBD

The sacral nerves are the five pairs of nerves in the colon and rectum's sacrum and control functions and contain autonomic and somatic efferent [32]. Moreover, afferent and efferent fibers are responsible for sensory perception and movements of the human body's lower extremities [32].

Sacral nerve stimulation is widely used as a therapeutic approach for neurogenic fecal incontinence. Holzer et al. (2008) showed improvement in the continence function in one patient who had undergone rectal resection for Crohn's Disease [33]. Brégeon et al. (2015) also evaluated the sacral nerve stimulation in a single patient with proctitis. In this study, the patient improved fecal incontinence and endoscopic and histologic proctitis activity scores over 18 months after permanent stimulation [34]. Moreover, the rectal barrier permeability measured in mucosal biopsies was reduced with sacral nerve stimulation, and junctional protein mRNA expression increased [34]. In addition, Vitton et al. (2008) showed that sacral nerve stimulation improved continence in five patients with Crohn's Disease with external and internal anal sphincter disruption [35]. After a follow-up time of approximately 14 months, the patients' quality of life increased significantly, while the Wexner scores and number of stools significantly decreased [35].

The exact mechanism of action of sacral nerve stimulation on IBD is still a matter of debate [36, 37]. Studies showed that sacral nerve stimulation determined satisfactory sphincter action, integrity, and function of several anatomic structures and changes in rectal sensitivity and motility [36, 37].

3.6 OTHER NERVES STIMULATED FOR IBD REMISSION

Kemler et al. (1999) reported the case of a patient with Ulcerative Colitis, combined with reflex sympathetic dystrophy, that was submitted to spinal cord stimulation [38]. The patient did not respond to conventional pain treatments (physical therapy, sympathetic blocks, and transcutaneous electrical nerve stimulation) suitable for spinal cord stimulation [38]. The complete system with a quadripolar electrode was implanted into the epidural space at the level of the vertebra C4. One and a half months after implantation and continuous stimulation, the patient showed Ulcerative Colitis manifestation characterized by nausea, distention, abdominal pain, bloody diarrhea, and

systemic symptoms such as weight loss and general malaise. A proctosigmoiditis erythema, with loss of vascular pattern but without superficial ulceration, was noted by sigmoidoscopy [38]. Fourteen months after implantation, the whole system was removed, and, interestingly, in the subsequent year, the Ulcerative Colitis has remained in remission [38]. Further research is needed to investigate the effect of spinal cord stimulation on IBD treatment.

Vitton et al. (2009) investigated transcutaneous posterior tibial nerve stimulation for fecal incontinence in IBD [39]. Twelve patients with IBD (seven Crohn's Disease, two undetermined colitis, three ulcerative colitis) were treated by transcutaneous posterior tibial nerve electrical stimulation. The treatment was followed up daily for three months, and then five patients (41.6%) reported a significant symptomatic and quality of life improvement [39]. Thus, this preliminary study suggests that posterior tibial nerve electrical stimulation may represent a new therapeutic approach to treating fecal incontinence in patients with IBD. However, more studies are required to confirm these results.

A recent Phase-III, placebo-controlled and randomized study investigated the effect of transcranial direct current stimulation on structural and functional changes in magnetic resonance imaging applied to ameliorate pain in IBD [40]. Thirty-six patients with IBD and chronic pain were stimulated for five days. After this elapsed time, the patients had pain reduction associated with changes in resting-state functional in magnetic resonance imaging [40]. Even though this approach is a non-invasive brain stimulation technique, this review was included to highlight a new IBD treatment option.

4 CONCLUSION

The bi-directional relation between the gastrointestinal tract and the central nervous system permits beneficial alternative therapies targeted at electrical nerves and brain stimulation. Many pre-clinical studies established the importance of electroceuticals for the neuromodulation of IBD. However, few clinical studies evaluated the effects of this option of treatment on IBD remission. More studies are necessary to standardize nerve parameters used to treat inflammatory conditions, mainly the duration, intensity, frequency of stimulation, and non-invasive neural stimulatory methods.

ACKNOWLEDGMENTS

The authors thank the Fundação de Amparo à Pesquisa do Estado de São Paulo [(FAPESP) process #20/06043-7 and process #20/08221-0]. The authors also thank the Conselho Nacional de Desenvolvimento Científico (CNPq) and Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto (FAEPA).

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

1. Collaborators GIBD. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020;5(1):17-30.

2. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46-54.e42; quiz e30.

3. Maduzia D, Matuszyk A, Ceranowicz D, Warzecha Z, Ceranowicz P, Fyderek K, et al. The influence of pretreatment with ghrelin on the development of acetic-acid-induced colitis in rats. J Physiol Pharmacol. 2015;66(6):875-85.

4. Coskun M. Intestinal epithelium in inflammatory bowel disease. Front Med (Lausanne). 2014;1:24.

5. Gombert M, Carrasco-Luna J, Pin-Arboledas G, Codoñer-Franch P. The connection of circadian rhythm to inflammatory bowel disease. Transl Res. 2019;206:107-18.

6. Digby-Bell JL, Atreya R, Monteleone G, Powell N. Interrogating host immunity to predict treatment response in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2020;17(1):9-20.

7. Jeong DY, Kim S, Son MJ, Son CY, Kim JY, Kronbichler A, et al. Induction and maintenance treatment of inflammatory bowel disease: A comprehensive review. Autoimmun Rev. 2019;18(5):439-54.

8. McLean LP, Cross RK. Adverse events in IBD: to stop or continue immune suppressant and biologic treatment. Expert Rev Gastroenterol Hepatol. 2014;8(3):223-40.

9. Payne SC, Furness JB, Stebbing MJ. Bioelectric neuromodulation for gastrointestinal disorders: effectiveness and mechanisms. Nat Rev Gastroenterol Hepatol. 2019;16(2):89-105.

10. Payne SC, Furness JB, Burns O, Sedo A, Hyakumura T, Shepherd RK, et al. Anti-inflammatory Effects of Abdominal Vagus Nerve Stimulation on Experimental Intestinal Inflammation. Front Neurosci. 2019;13:418.

11. Cheng J, Shen H, Chowdhury R, Abdi T, Selaru F, Chen JDZ. Potential of Electrical Neuromodulation for Inflammatory Bowel Disease. Inflamm Bowel Dis. 2020;26(8):1119-30.

12. Bonaz B, Sinniger V, Pellissier S. The Vagus Nerve in the Neuro-Immune Axis: Implications in the Pathology of the Gastrointestinal Tract. Front Immunol. 2017;8:1452.

13. Furness JB, Callaghan BP, Rivera LR, Cho HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. Adv Exp Med Biol. 2014;817:39-71.

14. Turner JR. Intestinal mucosal barrier function in health and disease. Nat Rev Immunol. 2009;9(11):799-809.

15. Chang JT. Pathophysiology of Inflammatory Bowel Diseases. N Engl J Med. 2020;383(27):2652-64.

16. Peyrin-Biroulet L. Anti-TNF therapy in inflammatory bowel diseases: a huge review. Minerva Gastroenterol Dietol. 2010;56(2):233-43.

17. Olofsson PS, Tracey KJ. Bioelectronic medicine: technology targeting molecular mechanisms for therapy. J Intern Med. 2017;282(1):3-4.

18. Harrison DG, Guzik TJ, Lob HE, Madhur MS, Marvar PJ, Thabet SR, et al. Inflammation, immunity, and hypertension. Hypertension. 2011;57(2):132-40.

19. Lindgren S, Lilja B, Rosén I, Sundkvist G. Disturbed autonomic nerve function in patients with Crohn's disease. Scand J Gastroenterol. 1991;26(4):361-6.

20. Lindgren S, Stewenius J, Sjölund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. Scand J Gastroenterol. 1993;28(7):638-42.

21. Clarençon D, Pellissier S, Sinniger V, Kibleur A, Hoffman D, Vercueil L, et al. Long term effects of low frequency (10 hz) vagus nerve stimulation on EEG and heart rate variability in Crohn's disease: a case report. Brain Stimul. 2014;7(6):914-6.

22. Kibleur A, Pellissier S, Sinniger V, Robert J, Gronlier E, Clarençon D, et al. Electroencephalographic correlates of low-frequency vagus nerve stimulation therapy for Crohn's disease. Clin Neurophysiol. 2018;129(5):1041-6.

23. Bonaz B, Sinniger V, Hoffmann D, Clarençon D, Mathieu N, Dantzer C, et al. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. Neurogastroenterol Motil. 2016;28(6):948-53.

24. Bhatti S, Jaafar I, Hassan H, Atassi H, Stocker A, Hughes M, et al. Effects of Gastric Neuromodulation on Crohn's Disease in Patients With Coexisting Symptoms of Gastroparesis. Neuromodulation. 2020;23(8):1196-200.

25. Sinniger V, Pellissier S, Fauvelle F, Trocmé C, Hoffmann D, Vercueil L, et al. A 12-month pilot study outcomes of vagus nerve stimulation in Crohn's disease. Neurogastroenterol Motil. 2020;32(10):e13911.

26. Bao CH, Liu P, Liu HR, Wu LY, Jin XM, Wang SY, et al. Differences in regional homogeneity between patients with Crohn's disease with and without abdominal pain revealed by resting-state functional magnetic resonance imaging. Pain. 2016;157(5):1037-44.

27. Steinman L. Elaborate interactions between the immune and nervous systems. Nat Immunol. 2004;5(6):575-81.

28. Tracey KJ. The inflammatory reflex. Nature. 2002;420(6917):853-9.

29. Rosas-Ballina M, Tracey KJ. Cholinergic control of inflammation. J Intern Med. 2009;265(6):663-79.

30. Tracey KJ. Reflex control of immunity. Nat Rev Immunol. 2009;9(6):418-28.

31. Tracey KJ. Understanding immunity requires more than immunology. Nat Immunol. 2010;11(7):561-4.

32. Callaghan B, Furness JB, Pustovit RV. Neural pathways for colorectal control, relevance to spinal cord injury and treatment: a narrative review. Spinal Cord. 2018;56(3):199-205.

33. Holzer B, Rosen HR, Zaglmaier W, Klug R, Beer B, Novi G, et al. Sacral nerve stimulation in patients after rectal resection--preliminary report. J Gastrointest Surg. 2008;12(5):921-5.

34. Brégeon J, Neunlist M, Bossard C, Biraud M, Coron E, Bourreille A, et al. Improvement of Refractory Ulcerative Proctitis With Sacral Nerve Stimulation. J Clin Gastroenterol. 2015;49(10):853-7.

35. Vitton V, Gigout J, Grimaud JC, Bouvier M, Desjeux A, Orsoni P. Sacral nerve stimulation can improve continence in patients with Crohn's disease with internal and external anal sphincter disruption. Dis Colon Rectum. 2008;51(6):924-7.

36. Matzel KE, Stadelmaier U, Besendörfer M. Sacral nerve stimulation. Acta Chir Iugosl. 2004;51(2):49-51.

37. Matzel KE, Kamm MA, Stösser M, Baeten CG, Christiansen J, Madoff R, et al. Sacral spinal nerve stimulation for faecal incontinence: multicentre study. Lancet. 2004;363(9417):1270-6.

38. Kemler MA, Barendse GA, Van Kleef M. Relapsing ulcerative colitis associated with spinal cord stimulation. Gastroenterology. 1999;117(1):215-7.

39. Vitton V, Damon H, Roman S, Nancey S, Flourié B, Mion F. Transcutaneous posterior tibial nerve stimulation for fecal incontinence in inflammatory bowel disease patients: a therapeutic option? Inflamm Bowel Dis. 2009;15(3):402-5.

40. Neeb L, Bayer A, Bayer KE, Farmer A, Fiebach JB, Siegmund B, et al. Transcranial direct current stimulation in inflammatory bowel disease patients modifies resting-state functional connectivity: A RCT. Brain Stimul. 2019;12(4):978-80.

41. Kemler MA, Barendse GA, Van Kleef M, Van Den Wildenberg FA, Weber WE. Electrical spinal cord stimulation in reflex sympathetic dystrophy: retrospective analysis of 23 patients. J Neurosurg. 1999;90(1 Suppl):79-83.