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Review Article

Efficacy of Faecal transplant technique (FMT) to manage Neuropathic pain

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Abstract:

Disorders of the somatosensory nervous system or neuropathic pain are associated with abnormal sensations called dysesthesia. Somatic symptom disorder is diagnosed when a person has a significant focus on physical symptoms, such as pain, weakness or shortness of breath, to a level that results in major distress and/or problems functioning. There is no specific treatment available, only intended to help control symptoms and to allow the person to function as normally as possible. Lately, FMT treatment showing some promising results.

Keywords: somatosensory; dysesthesia; neuropathic pain; faecal transplant technique

Introduction

Neuropathic pain or nerve pain (neuralgia) is a particular type of shooting, stabbing or burning sensation caused by damage or injury either to the nerves that send messages to your brain to signal pain, or to the brain itself may be worse at night, can be mild or severe but difficult to treat. At times a feeling is as sharp and sudden as an electric shock, very sensitive to touch or cold and also experience pain due to touch that would not normally be painful, such as something lightly brushing the skin. Neuropathic pain is characterized by abnormal hypersensitivity to stimuli (hyperalgesia) and nociceptive responses to non-noxious stimuli (allodynia) [1]. The conditions and the pathophysiological states that determine the onset of neuropathic pain are heterogeneous, such as metabolic disorders, viral infections and autoimmune diseases affecting the central nervous system (CNS). Nerve pain can affect any nerve in our body, but it commonly affects some nerves more than others such as post-herpetic pain, trigeminal pain, occipital pain and pudendal pain [2].

Nerve pain is associated with Sciatica (pressure on the nerves of the lower back that causes pain down your leg accompanied by pins and needles, numbness or weakness in your leg), Fibromyalgia (a chronic pain syndrome associated with burning or aching pain in different parts of your body due to unknown cause but triggered by emotional distress and poor sleep and genetic factors too), peripheral neuropathy developed by the peripheral nerves (nerves that that connect the brain and spinal cord to the rest of the body) are damaged due to diabetes, autoimmune diseases and other conditions. In addition an injury to brain, spine or nerves, poor blood supply to your nerves, heavy alcohol use, phantom pain after an amputation, vitamin B12 or thiamine (vitamin B1) deficiency, medicines, infections such as shingles and HIV/AIDS, multiple sclerosis, diabetes, stroke, cancer and its treatment with radiation, surgery, or chemotherapy, trapped nerves, such as in carpal tunnel syndrome could be also the causal factor for the prognosis of neuropathic pain especially fibromyalgia [3].

Diabetic neuropathy (DN) is painful if sugar is not under control ultimately resulting in the increase of morbidity and mortality. It often characterized by loss of sensation, pain, numbness, gait disorder, even amputation. The pathological mechanism involved in the development of DN remains unknown in spite of high prevalence rate. In the present scenario early detection of DN can only be achieved by assessing the nerve fibers, limited treatment with certain non-specific drugs with side effects and possibility of abuse [4].

Fibromyalgia affects up to 2% of general population. However, fatigue, chronic widespread pain non-refreshed sleep, mood disturbance and cognitive impairment such as forgetfulness, concentration difficulties, loss of vocabulary and mental slowness, among others are common, and have an important influence on quality of life that is challenging to diagnose and difficult to treat. In recent past this disorder is also associated with altered intestinal microbiota, suggesting that modulating gut microbiota could be an effective therapeutic treatment [5].

Global burden

Incidence and prevalence of neuropathic pain are difficult to estimate due to the lack of consensus on the definition of neuropathic pain globally. According to a systematic review of epidemiology of chronic pain,

prevalence between 3% and 17% was recorded, while the incidence was calculated in 3.9–42.0/100,000 person-years for post-herpetic neuralgia; 12.6–28.9/100,000 person-years for trigeminal neuralgia; 15.3–72.3/100,000 person-years for peripheral diabetic neuropathy (PDN), and 0.2–0.4/100,000 person-years for glossopharyngeal neuralgia. Moreover, neuropathic pain was more prevalent among women (60.5% of patients), reached a peak at 50–64 years of age, and was more frequently reported by manual workers, as well as among people from rural areas.

Management of Neuropathic pain

Most of the available treatments for neuropathic pain have moderate efficacy and present side effects that limit their use. Natural compounds have been investigated for their efficacy for the management of neuropathic pain similar to other diseases.

Several clinical studies suggest the efficacy of *Cannabis sativa* with around 100 cannabinoids was found to modulate neuropathic pain. Xie et al. [6] evaluated the effect of Puerarin a compound isolated from *Radix puerariae*, a potent antioxidant and anti-inflammatory agent used in traditional Chinese medicines for the myocardial and cerebral ischemia treatment [6]. Similarly, Qin, et al. in the same year investigated the analgesic effects of Gastrodin, a bioactive constituent of the traditional Chinese herbal medicine, in peripheral neuropathy [7]. Antihyperalgesic effect of the D-limonene (LIM-monocyclic monoterpene extracted from oranges and lemons) alone or complexed with β-cyclodextrin (βCD) was evaluated in an animal model of fibromyalgia. Kandhare and colleagues showed from their studies the possible involvement of the Azadirachta indica (AI), a tree of the *Meliaceae* family, in the treatment of peripheral neuropathy. The study results gave a promising hope for the possibility of the neuroprotective effect of AI for the treatment of neuropathic pain [8].

First-line treatments are based on the use of antidepressants and antiepileptic drugs. second- and third-line treatment are generally recommended to use Opioids due to their adverse related effects, while the strong opioids, oxycodone, and morphine are used in the third-line treatment [9].

FMT and neuropathy

Wealth of data now indicates that the gut microbiota has a connection with the central nervous system (CNS) and also participates in the regulation of cognition and pain, in addition to regulating peripheral and central sensitization [10]. The lipid metabolites of the gut microbiome has been linked to peripheral immune regulation, visceral pain, chemotherapy-induced pain), and fibromyalgia.

Development of Visceral hypersensitivity in patients is due to reduction in the abundance of butyrate-producing *Lachnospiraceae*, which is beneficial for the intestinal barrier. The members of this family of bacteria utilize lactate and acetate to produce butyrate via the butyryl-CoA or acetate CoA transferase pathways or the butyrate kinase pathway. *Roseburia hominis*, one such member proved to be a potential probiotic for treating stress-induced visceral hypersensitivity. In addition, by verifying the beneficial effect of butyrate-producing *R. hominis* on WAS rats, the results suggest that specific bacterial taxa or their metabolites are associated with visceral sensitivity and colonic barrier function. *Roseburia* has been considered to be a potential indicator of intestinal health, since alleviation of visceral hypersensitivity and increased caecal butyrate concentration after *Roseburia* administration. *Prevotellaceae* and *Coriobacteriaceae* increased, whereas that of *Peptococcaceae* decreased significantly after stress treatment. *Prevotellaceae* is reportedly involved in several intestinal diseases [11]. The literature survey indicates that only few studies have reported on the clinical application of microbes in neurogenic disorders.

The gut microbiota in diabetic neuropathy patients differ significantly from that of healthy controls [12]. Bäckhed F. et al. [12]. endorsed that FMT increased the insulin resistance from conventionally reared germ-free mice. Later Vrieze A. et al., [13] found an increase (median rate of glucose disappearance changed from 26.2 to 45.3 μmol/kg/min; $P < .05$) along with levels of butyrate-producing intestinal microbiota, six weeks after infusion of microbiota from lean donors, insulin sensitivity of recipients. The authors anticipated that intestinal microbiota could be developed as therapeutic agents to increase insulin sensitivity in humans also. Subsequently, Shen S., et al. [14] suggested that when FMT was performed on the appellate mice, the pain would be restored, indicating that the gut microbiota has an effect on neuropathic pain. Castelli V., et al. [15]. from another study found that probiotics alleviated the characteristics of paclitaxel-induced neuropathic pain *in vitro*, although their efficacy is dependent on the type of neuropathic pain. For instance, *Lactobacillus Reuteri* or *Bifidobacterium* were not effective against the neuropathic pain induced by chronic compression injury in rats.

Limited references are available for the efficacy of FMT on DN patients though they all gave the clue for positive results. Xu, HM. et al., [16] from their study reported a case of FMT to reach palliation of diabetic neuropathic pain and glycemic homeostasis.

Researchers showed from more than 8,000 gut microbiome profiles sampled from people in eight different countries abnormal changes in 19 bacterial species that are linked to increased risk of developing type 2 diabetes. Out of the 19 gut bacteria species identified, five were linked with type 2 diabetes alone and 14 with prediabetes and type 2 diabetes [17]. As reported in Nature Medicine, examples of the bacteria present at abnormal levels were higher levels of *Clostridium bolteae* and depleted *Butyrivibrio crossotus*. Low levels of the latter have been linked to obesity. This study included microbiomes sampled from 8,117 people (54% female)—1,851 with type 2 diabetes, 2,770 with prediabetes, and 2,277 control participants with normal blood sugar. To try and make the results as diverse as possible, the samples came from people in the United States, Israel, Sweden, Finland, Denmark, Germany, France and China. The investigators linked abnormal levels of 19 bacterial species to type 2 diabetes and/or prediabetes. Of these, 14 species had not previously been identified, whereas five had been linked to type 2 diabetes mentioned in the earlier research. The latter, included higher levels of *Clostridium citroniae*, *Clostridium bolteae* and *Escherichia coli*, and lower levels of *Coprococcus eutactus* and *Turicibacter sanguinis* in persons with type2 diabetes. The previously unidentified species included two oral *Streptococcus* species and *Bacteroides fragilis* all of which were higher in people with type 2 diabetes and are thought to trigger or add to inflammation in the body. *Prevotella copri* was also high in people with high blood sugar. It was suggested that changes to the microbiome may happen first, and diabetes develops later, not the other way around which is yet to be proved [18] (Table-1).

Impact of gut microbiota on insulin sensitivity and metabolic diseases have been reported earlier. Several pathways, including endotoxin, inflammation, gut-brain axis have been implicated on the functional significance. Gut-brain axis, a biaxial signalling axis between gastrointestinal tract and nervous system can regulate pain, behaviour and energy metabolism. Nervous system dysfunction through several mechanisms such as stimulation of host immune responses with cytokines as signalling mediators, synthesis of neuroactive metabolites and alteration of neuronal circuits by bacterial metabolites have been implicated earlier [19].

Bonomo RR. et al. [20] demonstrated that reshaping the gut microbiome of obese neuropathic mice by transplanting faeces from lean mice improved the pathophysiology of the disease by decreasing pain-associated behaviours and loss of nerve fibers in the skin. Modulation of peripheral nerve system (PNS) calcium signalling and immune cells concurrent to FMT-induced pain improvement was identified. In Rodent model, modulation of circulating butyrate is anticipated to be one of the underlying causes of this improvement in rodents. In parallel studies, they identified an association between lower circulating butyrate and distal pain in obese humans. They suggested that gut microbiome, circulating butyrate, a metabolite secreted by gut microbiome absorbed in the blood stream, may be involved by acting directly on peripheral nerve system immune cells and gene expression or pain channels.

In addition, they observed changes in expression of genes involved in lipid metabolism and calcium handling in cells of the peripheral nerve system (PNS). FMT were able to change the immune cell populations of the PNS.

Increase in the circulating short-chain fatty acid butyrate and pain improvement following FMT was also understood well. Butyrate could modulate gene expression ((neurons, macrophages, and Schwann cells) to modify neuronal hyper excitability and immune cells in the PNS. Surprisingly the circulating butyrate was also negatively correlated with distal pain in 29 participants with varied body mass index. Targeting the gut microbiota, butyrate, and its consequences may represent novel viable approaches to prevent or relieve obesity-associated neuropathies.

This study demonstrated that FMT can reverse early indices of sensory nerve dysfunction induced by a Western diet and suggested that FMT and potentially a metabolite secreted by the gut microbiota in the bloodstream, butyrate, can alter gene expression in PNS cells (neurons, macrophages, and Schwann cells) and modify neuronal hyperexcitability and immune cells of the PNS.

Shi, H., et al., [21]. Have explained from their studies how gut microbiota regulates peripheral and central sensitization. Changes in the gut microbiota profiles of rats (eg, broad-spectrum antibiotics treatment or FMT) gave a clue to assess the association between behavioral and inflammatory responses in Paclitaxel-induced peripheral neuropathy (PIPN) rats. The divers results from the indices showed that *Turicibacter, Clostridium sensu stricto 1, Corynebacterium, Bacteroides*, and *UCG-005* might exert certain effects on the development of PIPN. Two recent studies reported that the relative abundance of *Bacteroides*, and *UCG-005* may promote painful manifestations in rodents. In their study, the abundance of *Lactobacillus, unclassified Lachnospiraceae, Roseburia*, and *Eubacterium* was comparable among groups [21].

Thurm, T. et al., [22] successfully treated a 58-year-old patient diagnosed with fibromyalgia, and irritable bowel syndrome (IBS) who was non-responsive to variety of treatments over the years, suffered from significant social and occupational disabilities. He was suffering with severe diffuse pain, insomnia, diarrhea, abdominal pain, bloating, photophobia, hypersensitivity to odor, noise, light touch, tinnitus and palpitations. In addition, he had cognitive impairment such as memory loss, concentration deficit and depression with suicidal thoughts. Most of his symptoms started 18 years earlier at the age of 40. Since the patient was interested in FMT, but given that FMT is not approved for these indications, he used an online protocol for FMT screening and preparation and self-instilled the filtrate using an enema 6 times.

9 months after the last treatment, the patient reported full recovery of symptoms, going back to work at full time employment and FMT resulted in a gradual improvement of symptoms. Next generation sequencing analysis performed before the first FMT and after the last FMT of the enteric microbiota proportions gave a promising signature. Most prominent alterations at the genus level included a decrease in faecal Streptococcus proportion from 26.39% to 0.15% and an increase in *Bifidobacterium* from 0% to 5.23%. This case study substantiated as additional evidence for the effectivity of FMT in these functional disorders that are lacking an otherwise good medical therapeutic intervention. Significant decrease in the proportion of the Firmicutes phylum from 99.35% to 36.17% and an increase in the Bacteriodetes phylum from 0.42% to 39.82% post FMT was observed. At the genus level, faecal *Streptococcus* proportion fell from 26.39% to 0.15% and *Bifidobacterium* increased from 0% to 5.23%. Additional changes included bacterial diversity index that was reduced from 3.21 to 2.55 post FMTs and a negative stool culture for Candida. Faecal microbiota analysis performed prior and post FMT using A 16S rDNA genome sequencing demonstrating microbial composition alterations at the "Phylum" and "Family" level following FMT. % Pre FMT % Post FMT *Firmicutes* 99.35 36.17 *Lachnospiraceae* 47.6 5.37 *Ruminococcaceae* 2.74 10.16 *Clostridiaceae* 0.08 1.58 *Bacteroidetes* 0.42 39.82 *Actinobacteria* 0 13.44 Proteobacteria 0 0.76.

Irritable bowel syndrome (IBS) is a functional disorder characterized by abdominal pain or discomfort associated with defecation or change in bowel habits according to the Rome criteria. Investigations using standardized criteria reported 42% - 70% of fibromyalgia patients meeting IBS criteria and one study demonstrated 92% IBS in patients diagnosed with chronic fatigue syndrome CFS. Many patients report being diagnosed with fibromyalgia and later the diagnosis is converted to CFS and vice versa. Nevertheless, the authors were of the opinion that these results should be interpreted with caution, given that in addition to self FMTs, the patient underwent multiple additional interventions such as different dietary regiments, therapeutic trials with multiple medications, antibiotics and probiotics. This information based on different analysis techniques provides a wealth of information about the functional characteristics of the bacterial as well as management of the disorder in therapeutics. [23].

Minerbi et al., [24] performed a pilot study and analysed microbiota of 77 women with FM and that of 79 control participants and compared using 16S rRNA gene amplification and whole-genome sequencing. When comparing FM patients with unrelated controls using differential abundance analysis, significant differences were revealed in several bacterial taxa. Variance in the composition of the microbiota was explained by FM-related variables more than by any other innate or environmental variable and correlated with clinical indices of FM. In line with observed alteration in butyrate-metabolising species, targeted serum metabolite analysis verified differences in the serum levels of butyrate and propionate in FM patients.

All participants harboured without any discrepancy the predominant phyla including bacteroidetes (48% of total raw counts), firmicutes (40%), proteobacteria (4%), and actinobacteria (2%). Bacteroides genera, including Bacteroides dorei, Bacteroides uniformis, Bacteroides stercoris, Bacteroides ovatus, as well as Prevotella copri, Alistipes putredinis, and Faecalibacterium prausnitzii were the 10 most abundant specie.

Butyrate metabolism–related bacteria were altered in density such as *F. prausnitzii* and *B. uniformis* were found in less in relative abundance in FM patients, whereas higher relative abundance was observed for *Intestinimonas butyriciproducens*, *Flavonifractor plautii*, *Butyricoccus desmolans, Eisenbergiella tayi*, and *Eisenbergiella* massiliensis (Table-1).

When considering the 19 specific species identified as differentially abundant (DA) between FM patients and unrelated control participants, there was a broad range in how well characterised these species were. Within the gut, *F. prausnitzii* has been reported to exert antinociceptive as well as anti-inflammatory effects and to enhance the intestinal barrier function.

In contrast to the depletion of butyrate producers *F. prausnitzii and B. uniformis* in FM patients, Minerbi et al., [24] observed significant higher relative abundance of a number of other known intestinal butyrate producers: *I. butyriciproducens, F. plautii, B. desmolans, E. tayi,* and the recently identified *E. massiliensis*. Alterations in butyrate- and propionate-metabolizing species were further supported by alterations in serum levels of these short-chain fatty acids. Coherent with this putative shift in the butyrate-producing community of FM patients, Parabacteroides merdae was also significantly higher in relative abundance in FM patients.

Clostridium scindens and *B. desmolans*, 2 bacterial species capable of converting cortisol to androgens by 20α-hydroxysteroid dehydrogenase activity, were found in higher abundance in FM patients. Interestingly, abnormal regulation of hypothalamic-pituitary-adrenal axis has been reported in FM patients, although the direction of dysregulation is controversial. The combination of large cohort size with high depth of coverage allowed for the identification of low-prevalence DA species, such as *I. Butyriciproducens* (Table 1).

Gut biome before FMT	Gut biome of the patient	After FMT	REF
Acetanaerobacterium ,# *Acetivibrio, #* *Alistipes, #* *Anaerostipes, #* *Bacteroides, #* *Barnesiella, #* *Blautia, #* *Butyricicoccus, #* *Catenibacterium, #* *Clostridium, #* *Coprobacillus, #* *Coprococcus, #* *Dialistr, #* *Dorea, #* *Enterococcus, #* *Ethanoligenens, #* *Eubacterium, #* *Faecalibacterium, #* *Holdemania, #* *Howardella, #* *Lactobacillus, #* *Lactococcus, #* *Lactonifactor, #* *Leuconostoc, #* *Megamonas, #* *Megasphaera#* *Moryella, #* *Naaerofustis, #* *Odoribacter, #* *Oscillibacter, #* *Papillibacter, #* *Parabacteroides, #* *Roseburia, #* *Ruminococcus, #* *Sporobacterium, #* *Staphylococcus#* *Streptococcus, #* *Subdoligranulum, #* *Syntrophococcus ,#* *Turicibacter. #*	Associated: *Bacteroides fragilis,* *Clostridium sporogenes* *Corynebacterium glutamicum,* *Enterococcus* spp., *Escherichia coli,* *Lactobacillus, Lactobacillus fermentum KBL374* & *KBL375,* *Peptostreptococcus,* *Streptococcus* spp., **Increase** *Bacteroides fragilis*(oral) *[3] *Butyricicoccus desmolans*@ [24], *Clostridium bolteae* (type 2 diabetes), *Clostridium citroniae,* *Clostridium scindens* [24] *Eisenbergiella tayi*, 24] *Eisenbergiella massiliensis* [24] *Enterococcus* spp. *Escherichia coli,* *Flavonifractor plautii* @ [24], *Intestinimonas butyriciproducens,* [24] *Prevotella copri* [24] *Parabacteroides merdae* [24], *Streptococcus* sp. (oral) *[3], **Decrease** Bacteroides uniformis, @ [24], *Bifidobacterium* *Blautia faecis,* *Butyrivibrio crossotus* *Coprococcus eutactus,* *Faecalibacterium prausnitzii* @ [24], *Prevotella copri,* *Roseburia hominis*@ [11], *Turicibacter sanguinis* ,	**Increase** Bifidobacterium **Decrease** *Candida* *Streptococcus*	[16]Hao M.X. et al., (2021), [3] Healthdirect https://www.healthdirect.gov.au › nerve-pain. [22] Thurm, T. *et al.*, (2017). [24] Minerbi *et al.* (2019).

*Trigger or add to inflammation in the body. #Refer the analysis result after FMT treatment of fibromyalgia in the ref. [22]. @- (butyrate-producing bacteria)

Table 1: Microbiol (types of bacterial species) contents in Healthy, Neuropathic pain Patient and Patient after FMT

This first demonstration of gut microbiota alteration in no visceral pain, paves the way for further studies, elucidating the pathophysiology of FM, developing diagnostic aids and possibly allowing for new treatment modalities to be explored [24].

Subsequently Cardona D., et al., [5] performed a pilot randomized controlled trial in 31 patients diagnosed with Fibromyalgia syndrome (FMS) to compare the effects of a multispecies probiotic versus a placebo on cognitive variables (memory and attention) after eight weeks. Results showed that treatment with a multispecies probiotic produced an improvement in attention by reducing errors on an attention task, but it had no effect on memory. From vital information based on different clinical trials and case studies the gut microbiota was found to plays an important role in different physiological functions, exerting effects from energy metabolism to psychiatric well-being and negatively the higher aerobic enterococcal count, the worse the neurological and cognitive deficits, such as nervousness, memory loss, forgetfulness and confusion. These patients have an altered composition of SCFAs, and *Parabacteroides merdae* increasing neurotransmitters in FMS patients, responsible for cognitive dysfunction. The case study (self-performed FMT), in which FMT was extremely beneficial in a severely ill patient who suffered from a combination of three functional disorders-fibromyalgia, chronic fatigue syndrome and Irritable bowel syndrome. The patient had high levels of Candida and Streptococci that have normalized after the FMT [5].

To summarise from these review is that the role of FMT in improvement of **neuropathic** pain has a close link with the regulation of gut-brain axis, that FMT treatment might provide a possibility to explore potential therapeutic approaches in the management of disorders and its complications. FMT procedure also needs to be standardized about donor selection, stool preparation, delivery route, and dosing. Further studies to assess long-term outcomes are needed to provide better guidance on clinical decision-making, patient selection, and clinical practice. We conclude that randomized controlled trials are required to ground FMT as a possible successful therapy for these difficult-to-treat conditions.

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