Modifying the Collateral Symptoms in Patients with Parkinson's Disease

Chronic constipation is a common symptom among the general population and approximately 10–15% of people globally report having chronic constipation.[1] The presence of chronic constipation impacts the quality of life and hampers the work productivity of the individual.[2] Chronic constipation is either because of disorders of gut–brain interaction (DGBI), earlier known as functional gastrointestinal diseases, or due to organic causes attributable to mechanical obstruction, medications, metabolic diseases, and/or myopathic and neurological disorders. Up to 80% of patients with Parkinson's disease suffer from constipation which may precede the diagnosis.[3,4] The chronic constipation in patients with Parkinson's disease may occur because of sedentary habits or medications, and also because of hypomotility of the large intestine caused by loss of dopaminergic neurons in the enteric nervous system (ENS), autonomic dysregulation by deposition of Lewy bodies in dorsal nucleus of vagus nerve and various other brain regions, leading to variable combination of slow intestinal motility and pelvic floor dyssynergia.[5] Furthermore, the chronic constipation is also being modulated by depression and anxiety, which are often associated with Parkinson's disease.

Guided by the cost and the efficacy, treatment of chronic constipation is usually planned in a step-up approach that later becomes personalized depending upon subtype and the response to initial therapy. First-line treatment involves therapeutic trial with dietary changes, lifestyle modifications, and over-the-counter laxatives. Depending upon the response to treatment, the following sequence is recommended—osmotic laxatives (liquid paraffins, sorbitol, lactulose, and PEG) followed by stimulant laxatives (bisacodyl and sodium picosulfate), and next in the sequence are secretagogues (lubiprostone, linaclotide, plecanatide, and tenapanor).[6,7]

If symptoms do not improve, evaluation for pelvic floor dyssynergia and slow transit constipation should be instituted. For those having pelvic floor dyssynergia, pelvic floor rehabilitation and biofeedback therapy are recommended. Overall, 70% of patients will respond to biofeedback therapy.[8] Slow transit constipation can be treated by stimulant laxatives, prokinetic agents (prucalopride and Velusetrag) or in combination with secretagogues or osmotic agents.[7]

Despite the use of variety of medications, almost 50% of patients are not satisfied with the results,[9] therefore various targets are being explored including neuromodulation. The methods of neuromodulation in the spectrum of non-invasiveness to minimal invasiveness are whole-body vibration therapy induced via a noninvasive oscillation platform,[10] orally ingestible and programmable vibrating capsule[11] and neuromodulation created by transcutaneous interferential current therapy, transcutaneous tibial nerve stimulation, transcutaneous sacral nerve stimulation, percutaneous tibial nerve stimulation, and sacral neuromodulation (SNM).[12] Among all neuromodulation therapies, SNM has been popular and it involves placing an electrode in the third sacral foramen and then implanting a neuromodulator subcutaneously in the gluteal region after a percutaneous nerve evaluation as a screening test. The European Society of Neurogastroenterology and Motility guidelines on functional constipation in adults suggest that SNM may be tried in chronic refractory constipation.[13]

In the present study,[14] the authors have explored the therapeutic benefit of high-frequency repeated magnetic stimulation (HF-rMS), over sacral bone area in patients with Parkinson's disease having chronic constipation. After excluding any obvious secondary cause of cerebral injury/dysfunction and other systemic end organ diseases, 48 patients with Parkinson's disease were randomized equally into two groups, one which received HF-rMS (the intervention group) and other was a sham group. Their baseline data related to Parkinson's disease (both motor and non-motor symptoms) was meticulously recorded by using a battery of questionnaires/scales and were similar in both the groups. Constipation was assessed by using constipation score scale (KESS questionnaire). The primary objective was analyzed by comparing the reduction in the constipation score scale in both the groups pre- and post-HF-rMS therapy. The investigators showed that HF-rMS significantly improved not only the constipation score ($p < 0.05$) but also the motor functions, associated anxiety and depression, and overall quality of life ($p < 0.05$). The authors finally concluded that HF-rMS improved chronic constipation in patients with Parkinson's disease.

SNM was initially developed for the treatment of urinary incontinence way back in 1980s.[15] Subsequently, retrospective analysis showed additional benefits of this technique on the intestinal function, both in fecal incontinence and constipation.[16-18] The proposed hypothesis is that the SNM works by the stimulation of extrinsic nerve supply of the large intestine. It is more of a modulation than stimulation and involves a principle that activity in one neural pathway modulates the activity in another through synaptic interaction for optimized functionality.[19] SNM has been shown to increase pancolonic antegrade propagating pressure waves frequency in patients with slow transit constipation.[20] Since SNM has been observed to have efficacy in two diverse entities, i.e., incontinence and constipation, a role of central neuromodulation has also been proposed.[21]

Using percutaneous sacral nerve stimulation, Malouf *et al*.[22] have reported a 25% success rate in patients with idiopathic slow transit constipation. Kenefick *et al*.[23] in 2002 demonstrated increased bowel frequency from median of 1.1 (0.3–1.6) to 5.8 (1.3–9.3) evacuations per week along with improvement in Cleveland Clinic constipation scores from 21 (20–22) to 9 (1–20). Conversely in a Cochrane meta-analysis of two RCTs including 61 participants, SNM was not found to improve symptoms in patients with constipation.[24] A systemic review of seven studies, including 375 patients to assess the efficacy and harms of implanted SNM for adult patients with chronic constipation, reported pooled treatment success in 57–87% for patients receiving permanent sacral implants, although there was significant variation between studies. The morbidity rates were between 13 and 34% and with overall device removal rate between 8 and 23%.[25] Because of inconsistency in the outcome and poor selection of patients in various studies included in this systematic review, the authors suggested cautions in using sacral nerve stimulation in the management of chronic constipation. A single-centre follow-up study reported 1- and 5-year success rates of SNM of 87.5% (95% CI, 67.3–100.0%) and 31.2% (95% CI, 10.2–95.5%) respectively in patients having constipation.[26] A randomized double-blinded study of sacral nerve stimulation testing for chronic constipation showed poor results and the study was prematurely terminated due to high infection rate.[27] Currently, there are no predictors to identify patients with chronic constipation who will likely benefit from SNM.[28]

The most important consideration of the three RCTs evaluating the role of SNM in chronic refractory constipation, which is very relevant to this commentary, is the baseline population in which the SNM was tried. All the RCTs had patients with evidence of slow transit constipation with failed multiple lines of therapy including biofeedback in one. Results were unsatisfactory and suggest conduct of adequately powered trials before recommending SNM for the management of chronic refractory constipation.[29-31]

The investigators of the present study have provided a good set of baseline data of Parkinson's disease. However, besides constipation score scale, the baseline data of chronic constipation with respect to the previous treatment received, its efficacy, and duration is lacking. This seems important because it is judicious to use SNM only when other medical management of chronic constipation fails. Else, it is quite possible that patients who received magnetic stimulation therapy could have responded to up-titration/upgradation of medical management alone. Furthermore, it is important to know the baseline constipation score scale, and if possible, along with its severity classification, of both the groups, the intervention group and the sham group. This is important because it will help in identifying the severity subset of patients with constipation who are more likely to respond to this kind of therapy.

Overall, the present study is a welcome, more evidence is however required before positioning neuromodulation therapy in the management of chronic constipation in patients having neurological disorders including Parkinson's disease. Such therapy has relevance in dealing with chronic constipation in patients who opt not to take pharmacological treatment due to polypharmacy or other reasons.

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Conflicts of interest

There are no conflicts of interest.

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