Colonic manometry and sacral nerve stimulation in patients with severe constipation

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Abstract: The current treatment options that are available for patients with severe chronic constipation are unsatisfactory. Long-term high dose laxative therapy produces significant morbidity in some, with ongoing bloating and abdominal pain. In refractory cases subtotal colectomy has become increasingly popular. However this is a major abdominal procedure with all the normal associated risks. Less invasive procedures for the treatment of constipation are being sought. However, improved therapies can only stem from a better understanding of the phenomena underlying severe constipation. Colonic propagating pressure wave sequences (PSs) are responsible for discrete movements of content and are vital for normal defaecation. Deficiencies in PS frequency, amplitude and extent of propagation are all implicated in severe defaecatory dysfunction. Mechanisms that can normalise these aberrant motor patterns may help rectify the problem. Recently the novel therapy of sacral nerve stimulation (SNS) has been utilized for the treatment of severe constipation. The results from a limited number of studies are encouraging with improved stool frequency commonly reported. However, little is known of the effects of SNS upon colonic motor patterns. Colonic manometry provides the ideal test-bed to examine this phenomenon. Additionally colonic manometry can be used as a measurement tool to evaluate a range of stimulus parameters and determine those that give the optimal colonic response.

Key words: Constipation; Colonic manometry; Sacral nerve stimulation.

CONSTIPATION, EPIDEMIOLOGY AND HEALTH CARE BURDEN

Constipation, a common cause of morbidity, is estimated to affect between 15 and 27% of the western world. The prevalence increases to 30-40% of people aged over 65. Direct and indirect costs and resource utilisation are substantial. Chronic constipation in the US accounts for 13.7 million days of restricted activity and 3.4 million days of bed disability. The diagnosis and management of constipation leads to 5.7 million physician visits and 0.6 million hospitalisations per year, accounting for total costs of $US235M (2006 value). Drug costs are high with $US368M per yr (1985 value) being spent on the counter remedies and an additional $US22M per year spent on prescription drugs.

For many constipated patients laxative use will sufficiently alleviate their symptoms. However, for patients in whom laxatives do not restore normal bowel habit increased abdominal pain and bloating can result. Some patients, particularly those with obstructed defaecation can undergo a trial of biofeedback therapy, which can demonstrate significant improvement in quality of life and stool frequency. However, the long-term efficacy (>1yr) in patients with severe slow transit constipation is poor. Overall at least 36% of those presenting to the clinic subsequently fail non-surgical therapies (diet, bulking agents, laxatives, biofeedback). These patients can be extremely debilitating with physiological functioning, mental health, general health and bodily pain all scoring poorly on quality of life questionnaires in comparison to health. For such cases subtotal colectomy becomes an option. However as this is a major abdominal procedure it comes with all of the normal associated risks. In addition patients can develop post-operative small and large bowel complications such as intractable diarrhoea, small bowel obstruction, faecal incontinence and recurrent constipation.

COLONIC PROPULSIVE MOTOR PATTERNS IN HEALTH AND PATIENTS WITH CONSTIPATION

The cause of severe constipation remains undetermined; however abnormal colonic motor patterns are implicated. In health studies utilising combined colonic manometry and scintigraphy have shown that colonic propagating sequences (PS) and high amplitude propagating sequences (HAPS) are temporarily associated with discrete movement of colonic content. Studies in health also demonstrate that defaecation is preceded by a series of PSs and HAPSs in which the site of origin of each PS approaching stool expulsion moves in an orad direction (Fig. 1). These data indicate that defaecation is a complex process incorporating the entire colon. Indeed in health motor activity in the proximal colon is an essential component of defaecation. Our own studies have also demonstrated that this pre-defaecatory colonic response is absent in patients with obstructed defaecation.

It is recognised that both HAPSs and long-extent PSs are deficient or absent in severe slow transit constipation although the neural apparatus necessary for the generation of these motor patterns appears to be intact because intraluminal irritant laxatives can trigger them. This observation suggests that extrinsic or intrinsic factors capable of modulating the propulsive characteristics of PSs are likely to contribute to the pathogenesis of constipation. The actual mechanisms involved in the induction of these propulsive pressure waves are only partially understood.
The enteric nervous system provides the direct neuronal control of colonic motility, modulated through the sympathetic, parasympathetic and extrinsic afferent pathways. The vagal nerves provide parasympathetic innervation to the caecum, ascending colon and most of the transverse colon, whilst parasympathetic fibres from the second to the fourth sacral sections of the spinal cord innervate the distal part of the transverse colon, the descending colon and the rectosigmoid colon. Therefore intuitively, stimulation of pelvic nerves would be expected to have a motor response confined to the distal colon and ano-rectum. Yet evidence exists to suggest that stimulation of pelvic nerves is capable of inducing pan-colonic motor patterns. For example rectal chemical stimulation in the healthy human colon induces proximal colonic PSs presumably through long recto-colonic afferent pathways. This pathway appears to be blocked in at least one form of constipation.

It is possible that this attenuated pathway can be re-established through electrical stimulation of pelvic nerves. Indirect evidence supporting this hypothesis can be extrapolated from a case study in which a young female with severe constipation, received direct electrical stimulation to the sacral nerves is capable of inducing proximal colonic propulsive pressure waves from a canine colon suggested that electrical stimulation of sacral nerves can generated a similar colonic pre-defaecatory PS response to that observed during spontaneous defaecation. Taken collectively we can form the hypothesis that electrical stimulation of the pelvic floor nerves may be capable of inducing proximal colonic propulsive pressure waves in severe constipation, which in turn may improve constipation symptoms. This hypothesis prompted our lab to examine both the symptomatic and colonic response of the novel therapy sacral nerve stimulation (SNS) in a severely constipated cohort of patients.

**SACRAL NERVE STIMULATION IN CONSTIPATION**

The techniques of sacral nerve stimulation (SNS) and its use in patient’s with urinary and fecal incontinence has been documented in several recent reviews. Briefly, SNS is a minimally invasive surgical technique that allows for direct electrical stimulation of the sacral nerves S2-S4 via an electrode placed through the sacral foramen. Of the three sacral roots used S3, which contains afferent sensory, efferent autonomic motor nerves and voluntary somatic nerves, provides the most satisfactory clinical response. The SNS technique involves two stages. The first, commonly termed

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**Table 1. Sacral nerve stimulation in patients with constipation.**

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>No. of patients</th>
<th>Constipation Type</th>
<th>Intervention Technique</th>
<th>Study Design</th>
<th>Outcome Measure</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganio et al.</td>
<td>12 OD</td>
<td>PNE</td>
<td>Uncontrolled</td>
<td>Successful Evacuation Stool Frequency</td>
<td>66%* 25%</td>
<td></td>
</tr>
<tr>
<td>Malouf et al.</td>
<td>8 STC</td>
<td>PNE</td>
<td>Uncontrolled</td>
<td>Stool Frequency</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Kenefick et al.</td>
<td>4 STC</td>
<td>PNE &amp; Permanent</td>
<td>Uncontrolled</td>
<td>Stool Frequency</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Kenefick et al.</td>
<td>2 STC</td>
<td>Permanent</td>
<td>RCT</td>
<td>Stool Frequency</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Dinning et al.</td>
<td>8 STC</td>
<td>PNE</td>
<td>Uncontrolled</td>
<td>Coloc motor response Stool Frequency</td>
<td>100%* 75%*</td>
<td></td>
</tr>
</tbody>
</table>

* OD = Obstructed defaecation; STC = Slow Transit Constipation

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* P < 0.05

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Fig. 2. Iso-contour map of antegrade colonic motility in a patient with severe slow transit constipation, pre- and post sacral nerve stimulation. Each individual ridge represents an individual propagating sequence (PS) at the time the PS was initiated. The start of each ridge indicates the site of origin of the PS and the length of the ridge the extent of propagation of the propagating sequence. The shades of grey within each ridge represent the amplitude of each individual propagating pressure wave. The map highlights the dramatic increase in the frequency, amplitude and extent of propagation of PSs during sacral nerve stimulation.
the peripheral nerve evaluation (PNE), is conducted over two to three weeks and involves a temporary wire, with a single electrode, being introduced to the sacral root and con-
ected to an external stimulator. Patients that respond favour-
ably to the PNE move on to the second stage where a pulse
generator (Interstim®) connected to a timed lead with 4 ele-
ctrodes, is implanted permanently.37

In comparison to SNS use in urinary and faecal inconti-
nence, investigation of the effects of SNS in patients with con-
Constipation is still in its infancy. Only 4 previous studies
had been published each with a small sample size (<12).38-41
In such patients the data suggests that SNS can improve stool
frequency and reduce the percentage of time patients suffer
from bloating and pain. Importantly these studies also report
very few adverse events. However, it should be stressed that
the majority of these data are derived from the short-term
PNE phase (Table 1).

While SNS appears to influence stool frequency in con-
stituted subjects the in vivo effects of SNS upon colonic
function remained unknown. The only available data in
humans had come from previous studies of patients with
faecal incontinence, from which SNS had been shown to
alter ano-rectal motor function.32-43 In our own study of
SNS in severe constipation we used our validated technique
of pan-colonic manometry to simultaneously record colonic
motor patterns during periods of SNS.44 The data obtained
from this study indicates that SNS appears to induce both
proximal and distal colonic motor patterns. Furthermore we
observed an increase in the frequency of long extent PSs
and the frequency of HAPPs (Fig. 2). As mentioned above
these particular motor patterns are linked to both colonic
transit and defaecation in health. During the 3-week PNE
phase 75% of the patients reported improvement in stool
frequency (Table 1).

The mechanism of action of SNS in relation to initiating
pan-colonic motor patterns remains unknown. It is likely that
efferent neural pathways are activated but it is almost
certain that afferent pathways are also activated. The rapid-
ity of the colonic response to SNS45 is certainly compatible
with a neural pathway.

THE FUTURE OF SACRAL NERVE STIMULATION
IN PATIENTS WITH SEVERE CONSTIPATION

The reported positive outcome in carefully selected
patients, coupled with minimal adverse side effects suggests
that SNS is a reasonable option for patients who are faced
with surgical procedures such as a colecotomy in order to
relieve their constipation symptoms. In addition SNS, at
least in treating faecal incontinence, has been shown to be
highly cost effective in comparison to other surgical inter-
vention.47 However, further work is still required. As yet
only one randomized control trial has assessed the effects
of SNS in constipated patients and that study had a sample
size of two.48 Cleary data derived from adequately powered
randomised control trials and long-term follow-up in patients
with permanent implantation are still required. As is data
determining which patients may benefit form SNS treat-
ment.

In addition while a colonic response to SNS in constipa-
tion has been shown, the stimulation parameters necessary
to optimise this colonic response remain unclear. Assessing
the merits of various combinations of parameters (i.e. alter-
tation to pulse width, frequency and amplitude) can be time
consuming if the yardstick is a clinical response which can
take weeks or even months to develop.49 Measurement of
the immediate colonic contractile responses in the labora-
tory may prove to be a direct and powerful means of
evaluating a wide range of stimulus parameters in order to
help define the optimal ones.

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Supported by: NHMRC & Medtronic Australia.

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