Investigation into the effects of neuromodulation

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Abstract

Introduction: This thesis investigates the putative role of neuromodulation on bowel motility and the use of temporary neuromodulation as a tool for patient selection for permanent gastric neuromodulation. It also examines the durability of neuromodulation effects on the short and long-term basis.

Methodology: My preliminary studies involved a systemic review of different neuromodulations and assessment of GI motility with capsule endoscopy. After this I measured gastric emptying time, quality of life and nutritional status following temporary gastric neuromodulation (GNM) and permanent gastric neuromodulation.

Results: In our prospective study temporary and permanent gastric neuromodulation improved gastric emptying time, quality of life and nutritional intake of the patients.
An interesting result of my study was the validation of capsule endoscopy (CE) as a tool for assessing GI motility.

Conclusions:

1 GNM is an effective treatment option for the symptoms of drug-resistant gastroparesis.

2. Temporary GNM helps in patient selection for permanent GNM.

3. Capsule endoscopy may be used to assess GI motility.

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Abbreviations

AOI	Areas of interest
BPD	Biliopancreatic diversion
BPD-DS	Biliopancreatic diversion + duodenal switch
BSG	British Society of Gastroenterology
CE	Capsule endoscopy
CHO	Carbohydrate
CRPS	Complex regional pain syndromes
SCF	Cerebrospinal fluid
CT	Computed tomography
DM	Diabetes mellitus
EGG	Electrogastrography
FDA	Food and Drug Administration
GE	Gastric emptying
GES	Gastric electric stimulation
GI	Gastrointestinal
GNM	Gastric neuromodulation
GS	Gastric scintigraphy
HCL	Hydrochloric acid
IPG	Implantable pulse generator
IT	Intestinal transit
JIB	Jejunoileal bypass
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NSAID	Non steroidal anti inflammatory drug
OCTT	Orocaecal transit time
PCT	Primary Care Trust
PN	Parenteral nutrition
Ppm	Parts per million
QOL	Quality of life
RYGB	Roux-en-Y gastric bypass
SNM	Sacral neuromodulation
SCS	Spinal Cord Stimulation
T50	Gastric half-emptying time
TPN	Total parenteral nutrition
GSS	Gastroparesis symptom score
USG	Ultrasonography
VNS	Vagus-nerve stimulation
VFS	Vomiting frequency score/week

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Introduction of neuromodulation:

1.1 Neuromodulation:

Neuromodulation is the therapeutic alteration in the activity of central, peripheral or autonomic nervous system, electronically or pharmacologically with an implanted device.[1, 2] In recent years there has been increasing use of neuromodulation for various indications, namely deep brain stimulation for Parkinson's disease, Vagus nerve stimulation for epilepsy, sacral nerve stimulation for bladder and anal sphincter dysfunction and gastric stimulation for gastroparesis.

Neuromodulation is a technique, which originated from the observation that different intensities of electrical discharge, intended to induce paresthesia can induce analgesia or alteration in organ function. The basis of neuromodulation stems from the work of Melzack and Wall's gate control pain theory.[3] It was suggested that non-painful stimulus closes the 'gates' to the painful stimulus, which in turn prevents pain sensation from traveling to the central nervous system. The technique is still evolving.

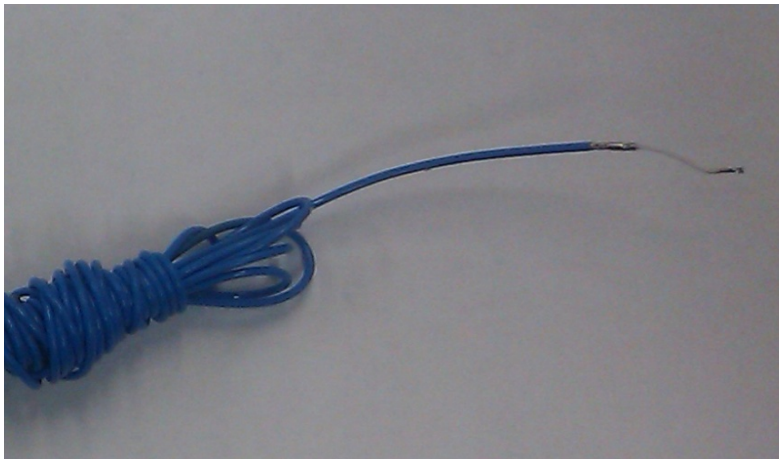
Its features like i.e. low risk, improved functional status and improved quality of life, makes neuromodulation an attractive therapeutic choice for physicians and surgeons. It is now frequently employed in resistant pain pathologies that are not well managed by conventional medical management or surgery.

In neuromodulation, as the term implies, neuronal activity of a group of neurons is 'modulated' by the release of one or more type of neurotransmitters by a single targeted neuron. This process is very similar in working mechanism to 'Fast synaptic transmission' where the post-synaptic neuron is influenced by a single presynaptic neuron.

In general, neuromodulation devices are comprised of three components. (Figure 1) The first component is the pulse generator, which is battery powered and can be externally programmed by either the patient or the physician. The second component consists of electrodes designed for implantation in the target neural tissue. The electrodes are of different sizes, lengths, and design, as required for percutaneous insertion or surgical implantation. The third component is the cable connecting the pulse generator

to the electrodes. Individual devices vary with respect to the location of the pulse generators and their programmability.

Pulse generator



Electrode with cable

Figure 1

1.2 Factors of effective neuromodulation:

For effective neuromodulation, there are certain factors, which influence neuromodulation mechanism.[4]

1. Characteristics of the tissue medium, which is offering electrical conductivity by an electrode.
2. The geometry of the electrode, which is selected for neuromodulation.
3. Anatomy of the neurons in relation to the electrode. The closer the neuron is to the electrode, the lesser signal it required for stimulation and vice versa.
4. Cellular factors related to a particular neuron. Distribution of ion channels on the neuronal membrane.
5. Factors related to the polarity, amplitude, and duration of a particular stimulus must be predetermined prior to giving neuromodulation.
6. Selection of the right electrode terminal. It has been reported in past studies that anode stimulus is effective in stimulating muscle fibers while cathode stimulus is preferable for activating neural fibers.

When studying neuromodulation, knowledge of chemical mediators that are known to regulate neuronal activity is crucial to understanding and manipulation for achieving effective therapeutics goals. Moreover, it is also essential to determine whether the neuromodulation is taking place in the relation to ‘one neuron one behavior' or one neuron multiple responses.

Chemical mediators that relay the information are termed ‘neuromodulators’. The largest group of neuromodulators includes neuropeptides. These neuropeptides although synthesized in neurons may or may not affect the neurons post-synaptically.

The exact mechanism of action of these devices is still not completely understood[1]. These devices generate high frequency/ low energy electrical stimuli, which are delivered to the target organ. They have effects on target organ as well as on the central nervous system.

1.3 Deep brain neuromodulation

Deep brain neuromodulation is a minimally invasive, targeted neurosurgical intervention that enables structures deep within the brain to be stimulated by an implanted pacemaker[2]. It has shown to provide clinical benefits for Parkinson disease (PD) and essential tremor (ET). Placement of high frequency stimulating electrodes in the region of the ventral intermediate nucleus of the thalamus (VIM) can markedly reduce tremor in these conditions, and stimulation of either the subthelmic nucleus (STN) or the internal segment of the globus pallidus (GPi) may not only reduce tremor, but also decrease bradykinesia, rigidity and gait impairment. [5]

Benabid et al [6] reported a large series of 117 patients with the ventral intermediate nucleus of the thalamus (VIM) stimulation for the treatment of tremor, with significant benefits.[7] Single and multicenter studies have consistently reported substantial benefit of VIM stimulation for ET with an average tremor reduction of over 80% in the majority of patients. [8,9,10]

The precise mechanism of action of deep brain neuromodulation is unknown. Possible explanations are as follows.

1. The cerebellar afferent receiving zone of the thalamus (human VIM nucleus) has been the primary target for the treatment of tremor. These nuclei receive excitatory glutamatergic afferents from the deep cerebellar nuclei excitatory glutamatergic afferents from the cerebral cortex and inhibitory GABAergic inputs from the reticular nucleus of the thalamus. The output from these nuclei primarily targets motor areas of cerebral but has also been shown to project to striatum. Thus, although it is common to view VIM as a simple relay for information from the cerebellum to cerebral cortex, the synaptic connections are complex and DBS likely influences multiple elements. [5,6]

2. High frequency stimulation of the STN in rodents increases extracellular glutamate in GPi and targets of STN projections,[12]

3. High frequency STN stimulation increases cyclic guanosine monophosphate (cGMP) in the GPi.[13]

These findings suggest that STN deep brain neuromodulation increases the neuropeptides out-put.

4. Haslinger et al[11] used positron emission tomography to measure flood flow responses and found that VIN DBS in ET patients at rest increased regional blood flow at the site of stimulation and in the sensory motor cortex in an increasing fashion corresponding to increasing stimulus frequency or amplitude.

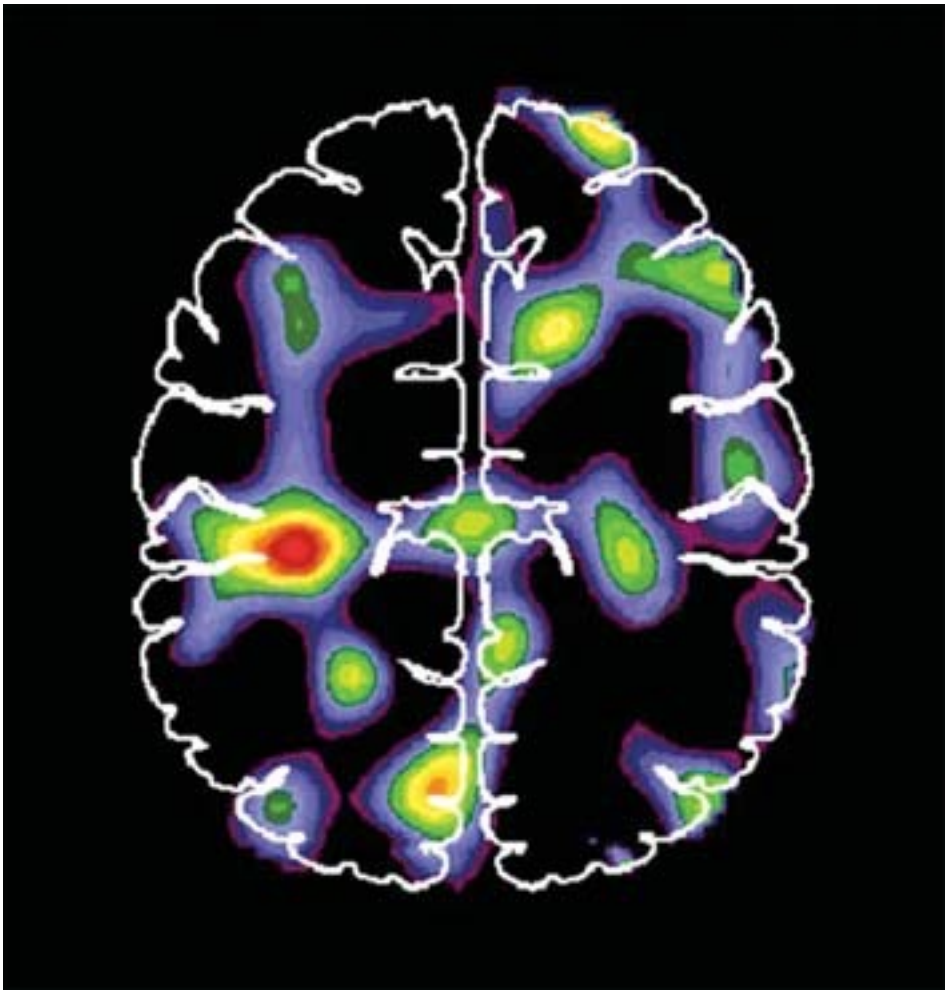


Figure 2

Blood flow changes associated with the presence of tremor or other movement of the upper extremities during 1-min positron emission tomography (PET) scans in patients (n = 8) with subthalamic nucleus deep brain stimulation (STN deep brain neuromodulation). The image represents an averaged change in blood flow comparing paired scans for each patient with STN stimulators off. [11]

Since its success with Parkinson's disease, the scope of deep brain neuromodulation has been expanded to other movement disorders (tremors, tics, and dystonias), psychiatric illnesses (major depression, obsessive-compulsive disorder), chronic pain, and refractory epilepsy.[3] To place the

stimulating electrode(s) in the targeted area, the surgeon uses a stereotactic frame with CT/MRI guidance. The wire electrodes are then tunneled subcutaneously from the head and neck to the chest wall where they are attached to a pulse generator. Adjustable settings of the pulse generator include, stimulation pulse amplitude, pulse width, and frequency. The patient may turn the device on or off and may switch between settings by using an external magnet.[14] Clinicians can also adjust stimulation parameters via telemetry to meet each patient's individual needs.

1.4 Vagus neuromodulation (VNM):

Vagus neuromodulation is used for drug refractory epilepsy. Epilepsy is characterised by recurring seizures. Different types of epilepsy have different causes. Epilepsy can be classified based on the origin of seizure. Seizures, which begin simultaneously in both hemispheres, are called generalised and when the seizure begins in one or more localised foci they are referred to as partial (or focal). Epilepsy has been estimated to affect between 362,000 and 415,000 people in England. Incidence is estimated to be 50 per 100,000 per year and the prevalence of active epilepsy in the UK is estimated to be 5–10 cases per 1000.[20] Two-thirds of people with active epilepsy have their epilepsy controlled satisfactorily with anti- epileptic drugs (AEDs). According to an observational study[21] in children and adult patients, approximately 30% of the population with epilepsy has inadequate control of seizures with AED. An Australian Health Technology Assessment (HTA) report observed that only 1% of the population with epilepsy is suitable for resective surgery.

Vagus neuromodulation (VNM) is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes adults whose epileptic disorder is dominated by focal seizures (with or without secondary generalisation) or generalised seizures. VNM is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes

children and young people whose epileptic disorder is dominated by focal seizures (with or without secondary generalisation) or generalised seizures.[21] Evidence suggests that with VNM >50% reduction in seizures can be achieved in 21-71% patients, with studies of long-term follow-up suggesting further reductions in seizures after 1 year, resulting in more than 1 in 3 patients experiencing >50% reduction in seizures.[22] Reductions in seizure severity and improved quality of life also occur in patients with a less significant change in seizure frequency, often making continuation with VNM worthwhile. However, some patients do not respond to VNM or may experience an increase in seizures. Unfortunately, the evidence available to date does not help predict those patients who will have the best outcomes. [16]Evidence suggests that surgical complications are rare, and that the majority of side effects are minor, stimulation related and improved with time or a change in stimulation parameters. Overall rates of sudden unexpected deaths are similar to those for the normal refractory epilepsy population - they have been reported to be raised for the first 2 years after VNM and then less than half normal rates for subsequent years. There is no evidence of increased mortality in patients with VNM compared with uncontrolled epilepsy.[20] Evidence on cost-effectiveness suggests that there are savings indirect medical costs following VNM that offset the cost of the procedure in approximately 3 years. The cost per Quality Adjusted Life Year (QALY) gained has been calculated as £4,785, assuming one response was obtained for every three implants (33%). [22]

The postulated mechanism of action involves the stimulation of afferent vagal nerve fibers that modulate cerebral neuronal excitability through the activation of either the limbic system or the noradrenergic neurotransmitter system, or through generalized brain stem arousal. The vagal nerve stimulation device is inserted subcutaneously below the left clavicle. The electrode is implanted into the left vagus nerve. This procedure is typically performed under general anesthesia.

1.5 Sacral neuromodulation:

Sacral nerves innervate the bladder, urethral sphincter and pelvic floor muscles. Sacral neuromodulation is used to treat the symptoms of an overactive bladder, including urinary urge incontinence and/or urgency frequency in patients who have failed or cannot tolerate conventional treatments.

In patients for whom conservative treatments have been unsuccessful, the standard alternatives include bladder reconstruction (such as augmentation and cystoplasty) and urinary diversion.

Sacral nerve stimulation involves applying an electric current to one of the sacral nerves via an electrode placed through the corresponding sacral foramen. The electrode leads are attached to an implantable pulse generator, which stimulates nerves associated with the lower urinary tract. Stimulation electrodes are placed at the level of the third sacral nerve (S3) and connected to an electrical stimulator that is implanted. Following a trial with a temporary stimulator that paces the bladder externally through the skin, patients with favourable results undergo surgical implantation of the permanent device, which consists of a wire containing four platinum electrodes. The wire is inserted surgically into the sacral foramen at S3 on one side adjacent to the sacral nerve. The generator itself is implanted subcutaneously in the hip area.[20]

Evidence from two randomised controlled trials (RCTs) [24,25] including a total of 50 patients with urge incontinence, showed that complete continence (completely dry with no incontinent episodes) or improvement of more than 50% in incontinence symptoms was observed in 50% and 80% of patients, respectively, following the procedure. This compared with 5% of patients in the control groups, who were receiving conservative treatments while waiting for an implant. In the one RCT [26] that reported on patients with urgency-frequency, an improvement of more than 50% in incontinence symptoms was observed in 56% (14/25) of patients, compared with 4% (1/25) in the control group. More evidence is available for patients with urge incontinence than for those with urgency-frequency.

The results of the case series studies included in the systematic review showed [27] complete continence and improvement in symptoms being reported in 39% (139/361) and 67% (338/501) of patients with urge incontinence, respectively, and 41% (22/54) and 65% (75/116) of patients with urgency-frequency, respectively. The benefits of sacral nerve stimulation were reported to persist for at least 3–5 years after implantation.

In general, evidence on the safety of this procedure was not well reported. Most complications observed in the studies were the result of technical problems related to implantation of the device. The results of the systematic review showed that, overall, the re-operation rate for patients with implants was 33% (283/860) [27.] The most common reasons for surgical revision were to replace or reposition implants due to pain or infection at the implant site, or to adjust and modify the lead system to correct breakage or migration.

Pain at the site of the pulse generator or at the site of stimulation was reported in 24% (162/663) [27] of patients, sometimes requiring replacement and repositioning of the pulse generator. Other complications included lead-related problems such as migration (16%), wound problems (7%), adverse effects on bowel function (6%), and infection (5%). No cases of long-lasting neurological complications were identified.

Sacral nerve stimulation for fecal incontinence

Faecal incontinence occurs when a person loses control of their bowel and is unable to retain faeces in the rectum. Faecal incontinence may result from dysfunction of the anal sphincter, which may be due to sphincter damage, spinal injury or a neurological disorder.

Faecal incontinence is associated with a high level of physical and social disability.

Typically, first-line treatment for faecal incontinence is conservative, such as anti-diarrhoeal medication and pelvic floor muscle training (including biofeedback therapy). In patients for whom conservative treatments have been unsuccessful, surgical alternatives include tightening the sphincter

(overlapping sphincteroplasty), creating a new sphincter from the patient's own muscle (for example, dynamic graciloplasty) or implanting an artificial sphincter. Some patients may require colostomy. Sacral nerve stimulation is a surgical treatment option for patients with faecal incontinence.

In patients with a weak but structurally intact sphincter, it may be possible to alter sphincter and bowel behaviour using the surrounding nerves and muscles. It involves applying an electric current to one of the sacral nerves via an electrode placed through the corresponding sacral foramen. Commonly, the procedure is tested in each patient over a 2- to 3-week period, with a temporary percutaneous peripheral nerve electrode attached to an external stimulator. If significant benefit is achieved, then the permanent implantable pulse generator can be implanted.

A recent systematic review [28] which included six case series studies reporting on 266 patients in total. In patients who had permanent implants, complete continence was achieved in 41–75% (19/46–12/16) of patients, whereas 75–100% (3/4–16/16) of patients experienced a decrease of 50% or more in the number of incontinence episodes. There was also evidence to suggest an improvement in the ability to defer defecation after permanent implantation. Patients also reported improvements in both disease-specific and general quality-of-life scores after the procedure.

Complications were reported both during the test peripheral nerve evaluation phase and after implantation. Evidence from the systematic review[28] indicated that of the 266 patients receiving test evaluation, 4% (10/266) experienced an adverse event. Fifty-six per cent (149/266) went on to receive permanent implantation. Of the patients who had permanent implants, 13% (19/149) reported adverse events. These included three patients who developed infections requiring device removal, seven patients who had lead migration requiring either relocation (five cases) or removal of the device, and six patients who experienced pain after implantation.

1.6 Phrenic neuromodulation

A diaphragmatic pacemaker electrically stimulates the phrenic nerve to cause rhythmic contraction of the diaphragm.[30, 31] Since its approval by the FDA in 1987, this device has been used to treat hundreds of patients with respiratory failure due to high cervical cord injury (C1–C2) or respiratory center dysfunction (central alveolar hypoventilation).[33] Successful implantation of the diaphragm pacemaker relies on an intact phrenic nerve and a functional diaphragm. Hence, patients with lesions of the phrenic nerve, its nucleus, or weakness of the diaphragm are not suitable candidates.[31, 32] Surgical implantation of a diaphragmatic pacemaker is usually performed laparoscopically. Four electrodes are implanted in each phrenic nerve. A receiver implanted in the subcutaneous tissue is connected to the electrodes by platinum leads. An external portable battery-operated transmitter generates radio waves, which are converted to an electrical stimulus by the receiver.[23] The amount of electrical voltage is proportional to diaphragm contraction or tidal volume. The transmitter controls the frequency of breaths, tidal volume, pulse interval, pulse width, and slope of a pulse.

1.7 Spinal neuromodulation (SNM):

The Spinal cord stimulation was first introduced in the 1960s. The common indications for spinal cord stimulation include failed back surgery syndrome (FBSS), complex regional pain syndromes (CRPS), peripheral vascular disease, and refractory angina.[33, 34]

People with FBSS continue to have back and/or leg pain despite anatomically successful lumbar spine surgery. It is not easy to identify a specific cause of neuropathic pain and people with FBSS may experience mixed back and leg pain. CRPS may happen after a harmful event or period of immobilisation (type I) or nerve injury (type II). Pain and increased sensitivity to pain are the most significant symptoms and are present in almost all people with CRPS. Other symptoms can include perceived temperature changes, weakness of movement and changes in skin appearance and condition.

The goal of treatment for chronic pain is to make pain tolerable and to improve functionality and quality of life. It may be possible to treat the cause of the pain, but usually the pain pathways are modulated by a multidisciplinary approach. This may include pharmacological interventions such as non-steroidal anti-inflammatory drugs, tricyclic antidepressants, anticonvulsants, analgesics and opioids. Non-pharmacological interventions, such as physiotherapy, acupuncture, transcutaneous electrical nerve stimulation and psychological therapies.

Spinal neuromodulation is a treatment for chronic pain that is usually considered after standard treatments (such as those described above) have failed. Spinal neuromodulation modifies the perception of neuropathic and ischaemic pain by stimulating the dorsal column of the spinal cord. Spinal neuromodulation is minimally invasive and reversible. A typical Spinal neuromodulation system has four components.

- A neurostimulator that generates an electrical pulse (or receives radio frequency pulses) – this is surgically implanted under the skin in the abdomen or in the buttock area.
- An electrode(s) implanted near the spinal cord either surgically or percutaneously (the latter via puncture, rather than through an open surgical incision, of the skin).
- A lead that connects the electrode(s) to the neurostimulator.
- A remote controller that is used to turn the neurostimulator on or off and to adjust the level of stimulation.

For FBSS, the British Pain Society (BPS) suggests that spinal neuromodulation may be an alternative to a repeat operation or increased opioid use. For CRPS, the BPS suggests that spinal neuromodulation may be considered after pharmacotherapy and nerve blocks have been tried but have not provided adequate pain relief. It is acknowledged that Spinal neuromodulation is not suitable for everyone with chronic pain, and that it should be used only as part of a multidisciplinary team approach with other

therapies and a strategy for rehabilitation. Re-intervention may be necessary to replace the spinal neuromodulation device because of complications (component failures, lead position or implant-related adverse events such as infection) or when the power source is depleted. On going care of patients is also required, which includes 24-hour availability for the investigation and management of potentially serious problems.

People selected for spinal neuromodulation normally have a stimulation trial to determine suitability for permanent implantation of a neurostimulator. This usually involves implanting the electrode(s) and leads with a temporary external device, which is used to mimic the effects of an implanted neurostimulator. A stimulation trial will assess tolerability (for example, of the stimulation sensation or the stimulation device) and the degree of pain relief likely to be achieved with full implantation.

Two RCTs investigated the effect of Spinal neuromodulation on the treatment of FBSS. One trial (PROCESS)[35] compared Spinal neuromodulation in combination with conventional medical management (CMM) and conventional medical management alone. The other trial compared spinal neuromodulation in combination with conventional medical management with repeat operation in combination with conventional medical management. Follow-up in the PROCESS trial was at 6 and 12 months, and in the other trial at 6 months and after a mean of 2.9 years. The primary outcome in both studies was the proportion of people who had 50% or greater pain relief.

The PROCESS trial reported that spinal neuromodulation had a greater effect than conventional medical management in terms of the proportion of people experiencing 50% pain relief at 6 months (48% and 9% in the Spinal neuromodulation and conventional medical management groups, respectively, $p < 0.001$) and 12 months (34% and 7% in the SCS and conventional medical management groups, respectively, $p = 0.005$). The other trial also reported a statistically significant benefit in terms of those experiencing 50% pain relief, favouring SCS in comparison with repeat operation (39% and 12% in the SNM and repeat operation groups, respectively, $p = 0.04$). In the PROCESS trial, opioid use did not differ significantly between the two groups (56% and

70% using opioids in the SNM and conventional medical management (CMM) groups, respectively, $p = 0.20$). However, the other trial reported that SNM resulted in a significantly greater number of people reducing or maintaining the same dose of opioids when compared with repeat operation (87% and 58% in the SNM and repeat operation groups, respectively, $p = 0.025$). In the PROCESS trial the SNM group showed a significantly greater improvement in function compared with the conventional medical management (CMM) group for mean change in functional ability as measured by the Oswestry Disability Index. The other trial reported no statistically significant differences between SNM and repeat operation for pain related to daily activities or neurological function. The PROCESS trial measured health-related quality of life (HRQoL) using the Short Form-36 (SF-36) and reported statistically significant benefits favouring SNM across all domains of the SF-36.

One RCT[36] investigated the effect of SNM in combination with physical therapy compared with physical therapy alone for the treatment of type I CRPS. The people in this trial were followed up at 6, 24 and 60 months. The primary outcome was change in pain intensity from baseline.

This trial reported that SNM in combination with physical therapy was more effective than physical therapy alone in reducing pain, measured as mean change on a visual analogue scale (0–10 cm) at 6 months (–2.4 cm and 0.2 cm, respectively, $p < 0.001$) and at 2 years (–2.1 cm and 0 cm, respectively, $p = 0.001$), but not at 5 years (–1.7 cm and –1.0 cm, respectively, $p = 0.25$). No statistically significant differences were identified between the SCS and physical therapy groups for improvement in time taken to perform tasks using the affected hand or foot. There were also no statistically significant differences for HRQoL at 6 months (percentage change in HRQoL: 6% in the SCS group and 3% in the physical therapy group, $p = 0.58$) or 2 years (7% in the SCS group and 12% in the physical therapy group, $p = 0.41$).

A subgroup analysis which included only those people who received their allocated treatment, reported that SNM in combination with physical therapy was more effective than physical therapy alone in reducing pain, measured as

mean change on a visual analogue scale at 5 years (–2.5 cm and –1.0 cm, respectively, p = 0.06).

Patients selected for this therapy are those who are refractory to conventional medical management and surgical therapies. Though multiple mechanisms have been explored, the exact mechanism activating spinal cord neuromodulation is poorly understood[36] In the early years, the plated type leads were surgically implanted directly over the spinal cord via laminectomy. Such method leads to undesirable complications including cerebrospinal fluid (CSF) leakage, localized fibrosis, and arachnoiditis. To avoid these complications, it was suggested to implant the leads in the epidural space. Subsequently, the less-invasive percutaneous technique via a modified Tuohy epidural needle was introduced. The percutaneous system allows insertion of the lead without the laminectomy. Moreover, the technique easily allows a trial stimulation to assess suitability for a permanent implant. If the patient is selected as a candidate for permanent implant then, an internal pulse generator is implanted as a separate procedure. The site of electrode placement depends on the site of pain. In general, the electrode is placed at the T9-L1 level for lower limb pain, C6 to T2 for angina and C4 to T1 for upper limb pain.

Conclusion:

Neuromodulation has been useful in different parts of the body for variable conditions. It was primarily used, as an alternative modality after first line treatment was unsuccessful. It was generally implemented after successful trial period.

2. Gastroparesis

2.1 Definition:

Gastroparesis is a syndrome of objectively delayed gastric emptying in the absence of mechanical obstruction and cardinal symptoms including early satiety (feeling full after very little intake of food) and postprandial fullness (feeling full after meal) nausea, vomiting, bloating and upper abdominal pain.[38]

The three most common aetiologies include[39]:

1. Diabetes mellitus (29%)
2. Post surgical (13 %)
3. Idiopathic (36%)

Other causes of gastroparesis have been described in the literature. They include intra-abdominal malignancy, eating disorders, chronic renal failure, muscular dystrophy and medications including atropine, opiates, tricyclic antidepressants, phenothiazines, calcium channel blockers and lithium.

Although the epidemiology of the disorder is not well known, the majority of patients are young and middle-aged women. Gastroparesis in diabetic patients interfere with oral drug absorption and impair blood glucose level, leading to further complications with ineffective blood glucose control.

Gastroparesis is a debilitating condition, which can reduce a functional individual to an existence tied to hospitals and emergency rooms. Gastroparesis patients are prone to life-threatening complications, such as electrolyte imbalance, dehydration and malnutrition. Soykan et al,[42] in their analysis of 146 patients seen over six years in 2 centers, with mean duration of symptoms for 12 years, indicate that 10% of patients died during the follow-up period. They describe gastroparesis as "far from being a benign disorder".

2.2 Disease prevalence

The true prevalence of gastroparesis is not known; however, it has been estimated that up to 4% of the population experiences symptomatic manifestations of this condition. Prevalence of gastroparesis is increased in diabetic patients and may occur in 30–50% of patients with long term diabetes mellitus type 1. [67, 68]

The most frequently reported symptoms of gastroparesis include nausea, vomiting, early satiety (feeling full after very little intake of food) and postprandial fullness (feeling full after meal). Abdominal discomfort and pain are also reported. Weight loss, malnutrition and dehydration may be prominent in severe cases.

Females are more commonly affected with female to male ratio of 4:1. The idiopathic type of gastroparesis is the most common cause up to 36%, followed by diabetes (29%) [58] The data reported here is from large historical follow-up but similar data from other parts of the world is scarcely available so ethnic prevalence cannot be conclusively drawn.

Diabetes is one of the major accountable causes of gastroparesis. The prevalence is more common in type 1 Diabetes mellitus, around 30-50%, followed by 15-30% in type 2 DM.[55-57]

Gastroparesis has a negative impact on a patient's quality of life, assessed by health related quality of life survey form (SF36). It is also associated with significant costs both to patients and healthcare services. In addition, to the cost of drug therapy, patients with severe symptoms face repeated hospital admissions and often rely on supplemental feeding.

In 2002 Aamir et al[95] reviewed medical charts of 236 patients with symptomatic gastroparesis over 3 years and found that 24.8% of the patients

were hospitalised at least once for symptoms of gastroparesis and 36.8% of those patients required four or more hospitalisations. The same study reported that 18% of the studied patients stopped working because of their symptoms.

Hospitalisation was also highlighted in several clinical trials. Forster et al [48] reported that gastroparesis patients involved in their study were hospitalised an average of 6 times in the year before GNM therapy. The patients involved in McCallum et al [64] study were hospitalised for a mean of 31 days (range 0–200 days) in the year before GNM therapy.

In addition to hospitalisation, many gastroparesis patients required regular nutritional support. The main categories of support are total parenteral nutrition (TPN) or enteral nutrition (EN). A few studies examined the cost of nutritional support in the UK and the USA from the health service perspective their results clearly demonstrate that nutritional support (even if delivered in a home setting) required very significant expenditure. The alternative hospital treatment (TPN) cost on average $150 per day [48]

Finally, severe gastroparesis has a negative impact on the patient's ability to perform regular activities, including work. Revicki et al,[53] in their 2003 study, reported statistically significant positive correlation between patient-reported symptom severity (measured by the gastroparesis symptom score) and the number of disability days and the number of days with restricted activity. The lost productivity is an additional cost born both by the patient (lost earnings) and society.

2.3 Mortality & Morbidity:

Gastroparesis can lead to reduced oral intake, as disease advances with time it can progress to nutritional deficiencies and worsens their prognosis.[54]

There is, therefore, a clear need for cost-effective alternative treatment for these severely sick patients who are not responding to current therapies and

who could only be managed with nutritional support[48] (which is expensive and carries a high risk of infection) or irreversible surgery.

Gastric neuromodulation is considered a safe, reversible and cost-effective treatment alternative for patients suffering from chronic, drug-refractory nausea and vomiting secondary to gastroparesis.

There is conflicting data about the effectiveness of GNM.

It has been shown to:

- Reduce nausea and vomiting and improve quality of life. [69,70,74, 75,76,77,78,79,80,81]
- Improve glucose control in diabetic patients. [70, 76,80]
- Reduce the use of nutritional support and health care costs needed for hospitalisations. [69,70,71,74,76,78]
- RCT conducted in 2003, did not conclusively showed significant improvement. [56]
- T Abell at el,[62] showed no significant change in ON and OFF period in a double masked placebo controlled trial.
- Macullum at el [66] showed no change in symptoms and GE.

2.4 Clinical Presentation:

The symptoms are often the same with the different etiologies of gastroparesis: nausea, vomiting, early satiety, and postprandial fullness [74] In 416 patients from the NIH Gastroparesis Registry, symptoms prompting evaluation more often included vomiting for diabetic gastroparesis (DG) and abdominal pain for idiopathic gastroparesis (IG). Patients with IG have more early satiety and abdominal pain compared with patients with DG who have more severe retching; all the patients included in these multicenter studies had documentation of delayed gastric emptying in their medical record [64,68]

The predominant symptom presentation divides gastroparesis into three types; [59]

1. Vomiting Predominant Gastroparesis (diabetic gastroparesis)
2. Dyspepsia Predominant Gastroparesis (idiopathic gastroparesis)
3. Regurgitation Predominant Gastroparesis

2.5 Causes of Gastroparesis

Gastroparesis can result from several causes. The three most common aetiologies are DM, post surgery and idiopathic. [59]

Diabetic Gastroparesis: Gastroparesis in diabetic patients has been well documented. Most often it affects patients with long-term diabetes. Gastroparesis can cause reduce oral intake which may result in poor glycemic control. High blood glucose further delays the gastric emptying time and it can lead further poor oral intake and worsening of the glycemic control. [76]

Post-surgical gastroparesis:
In the past, most cases resulted from vagotomy performed in combination with gastric drainage to correct medically refractory or complicated peptic ulcer disease. Since the advent of laparoscopic techniques for the treatment of gastoesophageal reflux disease (GERD), gastroparesis has become a recognized complication of fundoplication (possibly from vagal injury during the surgery) or bariatric surgery that involves gastroplasty or bypass procedures. The combination of vagotomy, distal gastric resection, and Roux-en-Y gastrojejunostomy predisposes to slow emptying from the gastric remnant and delayed transit in the denervated Roux efferent limb. The Roux-en-Y stasis syndrome — characterized by postprandial abdominal pain, bloating, nausea, and vomiting — is particularly difficult to manage, and its

severity may be proportional to the length of the Roux limb (generally, 25 cm is ideal to avoid stasis).

Post-surgical gastroparesis has been treated successfully in some centers. In one study, six post-Roux-en-Y gastric bypass patients developed gastroparesis. They were treated successfully with GNM, and it resulted in improved symptoms of nausea and vomiting. Furthermore, improved GE was also recorded. [82]

Post-esophagectomy delayed GE was treated with GNM in two patients. [83] Improved symptoms (including nausea, vomiting and total symptom score) were recorded after GNM.

Idiopathic gastroparesis: Idiopathic Gastroparesis is diagnosed in patients with no cause of gastroparesis identified on extensive investigations. [84, 85] The role of gastric neuromodulation in successful treatment of such patients has been described in published literature. [48, 80,86]

2.6 Pathogenesis of Gastroparesis:

The gastrointestinal tract comprises of longitudinal and circular smooth muscle that undergoes coordinated movement for the purpose of meal accommodation, effective digestion of meals, gastric secretions and timely emptying of the gastric contents to the duodenum and other areas and signals to halt digestive process as required. Any disorder in this so called ‘neuromuscular loop' will logically affect the downstream functions of varying intensity. One of the outcomes of this disorder includes gastrointestinal dysmotility, which in severe cases significantly affect patient's health status and quality of life and may induce nutritional malabsorption and deficiencies. The current therapies including prokinetics, intrapyloric botulimun toxin injection, only transiently relieve symptoms. [30,72,73,74]

2.7 Pathophysiology of Gastroparesis:

Gastrointestinal, muscular movements are coordinated extrinsically as well as intrinsically. The intrinsic components include the smooth muscle, interstitial cells of Cajal, Enteric nervous system (ENS) that is within the wall of the gastrointestinal tract.

The ENS contains 200-600 million neurons, distributed in many thousands of small ganglia, the great majority of which are found in two plexuses, the myenteric and submucosal plexuses. The myenteric plexus forms a continuous network that extends from the upper esophagus to the internal anal sphincter. Submucosal ganglia and connecting fiber bundles form plexuses in the small and large intestines, but not in the stomach and esophagus. The connections between the ENS and CNS are carried by the vagus and pelvic nerves and sympathetic pathways.

The relative roles of the ENS and CNS differ considerably along the digestive tract. Movements of the striated muscle esophagus are determined by neural pattern generators in the CNS. Likewise the CNS has a major role in monitoring the state of the stomach and, in turn, controlling its contractile activity and acid secretion, through vago-vagal reflexes. [76]

The extrinsic component comprises of the endocrine subcomponent that includes the pancreatic cells and other endocrine cells spread all over GIT and a neural subcomponent that include vagus nerves and sympathetic neurones. Taking into account the intrinsic component generally and the interstitial cells of Cajal specifically, it is involved in the generation of electrical pulses that in turn contribute to tone generation and other mechanical signals.[45] The interstitial cells of Cajal act like 'pacemaker of heart', generating phasic electric signals, which in turn elicit wave of contraction from gastric corpus (main body) and antrum.[60] Degenerative changes due to different causes like diabetes or idiopathically can induce gastroparesis by the dysfunction of both the intrinsic and extrinsic components.[60]

2.8 Investigations:

2.8.1 Gastric Scintigraphy. (GS)

Gastric emptying scintigraphy of a solid-phase meal is considered the standard for diagnosis of gastroparesis, as it quantifies the emptying of a physiologic caloric meal. The gastric emptying (GE), and the rate of GE at any given point during the test can be calculated. Some clinicians have proposed to perform solid and liquid phase scintigraphy. Most centres use 99m Tc (radioactive material) mixed with egg sandwich as a test meal. In the past, different meals have been used for assessment of GE, including beef liver (radioactive labelled), chicken liver (radioactive labelled) and low-fat meal (radioactive labelled). However, egg sandwich is readily available, easy to cook and more physiological compared to other meals. 100–120-minute GS should be for the evaluation of GE and the test can be extended to 4–6 hours for the assessment of intestinal transit time. It is considered that solid GE shows a lag phase (no/little GE) followed by GE. Certain drugs may affect GE including opiates (to slow GE) and prokinetic and macrolides (to enhance GE). Also, Ca channel blockers, K channel blockers, laxatives and other medication may affect GE. It is therefore recommended that such medicines should ideally be stopped 2–3 days before the test. GS results vary in each patient, and they may differ in same patient at different times. Also, other factors such as gender, smoking and phase of the menstrual cycle may also influence the GS results.

After radioactive labelled meal intake, an area of interest is drawn around the stomach. Data points are corrected for decay, movements and skin marker (if used). Anterior and posterior acquisitions are calculated within the area of interest, and a geometric mean is calculated for each data point. It is, however, one disadvantage of GS that there is radiation exposure even though the dose used in GS is very small. GE time can be described in terms of gastric half-emptying time (T50) and total emptying can also be calculated.

An area of interest around the stomach is drawn in both anterior and posterior pictures, during gastric scintigraphy and then gastric half-emptying time (T50) is calculated

Normal gastric half-emptying time (T50) was (99 ± 26 minutes) based on a study in healthy volunteers.[98]

2.8.2 EGG (electrogastrography):

EGG measures the myoelectric activity of the stomach. Gastric slow waves are detected by the skin electrodes on the abdominal wall. The frequency, pattern and intensity of myoelectric activity are recorded. [86]

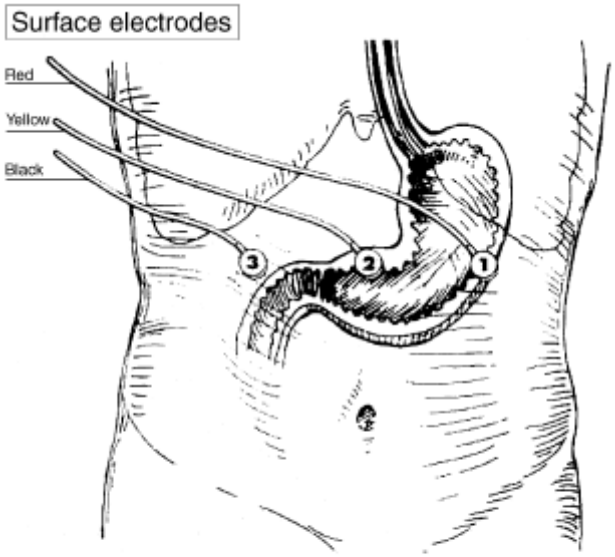


Figure 1 One commonly used electrode placement for electrogastrography recording is shown. Active electrodes are positioned below the left costal margin and, between the xyphoid process and umbilicus. The electrode positioned in the right upper quadrant is a reference or common electrode.

Figure 3: Electrogastrography (EGG)
Adapted from Parkman et al [86]

The EGG results are described in terms of bradygastria, tachygastria or normal. Normally, gastric myoelectric activity is recorded as 2–4 cycles/min. An increase >4/min is called tachygastria and a decrease <2/min is classified as bradygastria

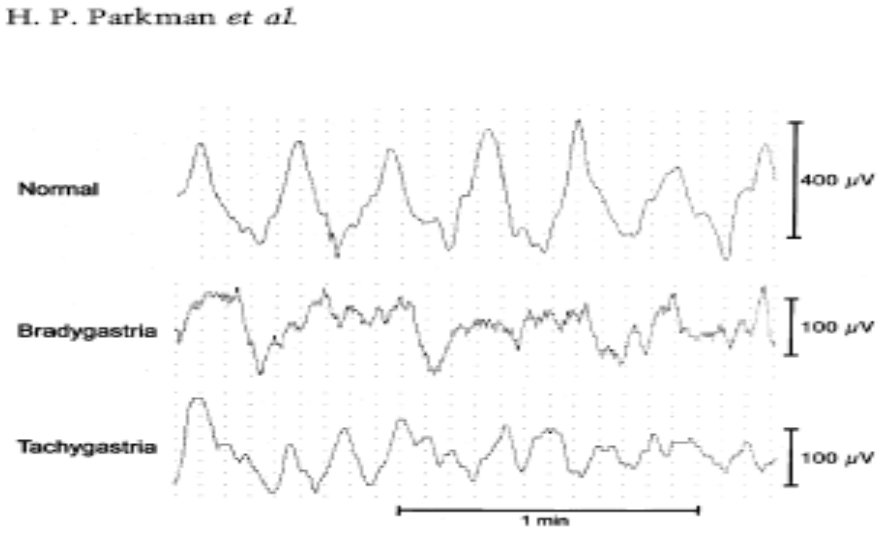


Figure 4: Gastric electrical activity on EGG Adapted from Parkman et al [86]

This procedure is not part of routine clinical care. Patients are required to stay still and small movement results in artefact and can invalidate the results.

2.8.3 Antroduodenal manometry:

This procedure is used to assess duodenal and lower gastric motor function and is described in terms of the origin and propagation of migratory motor complex (MMC). These complexes occur in three phases: Phase 1 (no or little activity); Phase 2 (MMC irregular activity/spike potentials); and Phase 3 (MMC strong expulsive movement produced to push the food from the distal stomach to the duodenum). An abnormal Phase 3 MMC is considered significant finding to suggest motility-related problems. The test should ideally be performed in fasting and postprandial states. This test has not been validated and needs more research for routine clinical use. Besides, the intolerance of electrodes in the GI tract and wire migration/displacement may also invalidate the results. [85.88]

2.8.4 Ultrasonography (USG):

GE can be assessed by transabdominal USG. This is done by serial changes noted by USG in the antral part of the stomach. It can also determine the gastric wall movement. The antral blood flow can also be assessed by duplex. This is not a widely accepted method as it is operator dependent; difficult to perform in obese subjects and examination can be difficult due to the presence of air in the stomach and transverse colon. This is not a validated method for this purpose.[88]

2.8.5 Magnetic resonance imaging (MRI):

Trans axial MRI scans performed after every 15 minutes can be used to detect gastric accommodation and GE. The advantages of this method include no exposure to radiation; however, it is very time consuming and quite expensive. Therefore it is not widely used except in experimental studies. [86.88]

2.8.6 Capsule endoscopy:

Capsule endoscopy is mainly used for the assessment of occult GI bleeding. However, its utility as a tool to assess GI motility is not widely explored. The patient swallows a small capsule, usually after an overnight fast. The capsule consists of a camera, a light source and a wireless circuit for the acquisition and transmission of signals. As the capsule moves through the gastrointestinal tract, images are transmitted to a data recorder, worn on a belt outside the body. These data are transferred to a computer for interpretation. The capsule is then passed in the patient's stool and not used again.

Details of the study of capsule endoscopy for GI motility are described in chapter 3.

2.9 Nutritional and economic implications of gastroparesis

In up to 40% of the patients with gastroparesis [82], they have poor oral intake which can leads to malnutrition. Oral medications are some times ineffective or intolerable. Treatment options for these drug-refractory gastroparesis patients include nutritional support in the form of enteral nutrition (EN) or total parenteral nutrition (TPN), which poses a high financial burden (upto $150 per day), or gastrectomy as a final resort.

Soykan et al[42] showed that 22% of gastroparesis patients required short- or long-term enteral feeding via laparoscopic placement of a jejunostomy tube for nutritional support at some point during the study. A few studies examined the cost of nutritional support in the UK and the USA from the health service perspective.[56] Their results clearly demonstrate that nutritional support (even if delivered in a home setting required very significant expenditure. The alternative hospital treatment (TPN) is even more costly.

2.10 Current treatment options

2.10.1 Medical

The primary goals of existing treatments are symptomatic relief and restoration and maintenance of adequate nutrition. Current treatment options include dietary modifications and the use of prokinetics and antiemetic. In up to 40% of gastroparesis patients, these drugs are ineffective or intolerable.[82, 91]

2.10.2 Nutritional

Gastroparesis can lead to poor oral intake, a calorie-deficient diet, and deficiencies in vitamins and minerals.[82,83] The choice of nutritional support depends on the severity of disease. In mild disease, maintaining oral nutrition is the goal of therapy. In severe gastroparesis, enteral or parenteral nutrition may be needed. For oral intake, dietary recommendations rely on measures that optimize gastric emptying such as incorporating a diet consisting of small meals that are low in fat and fiber. Since gastric emptying of liquids is often preserved in gastroparesis, blenderized solids or nutrient liquids may empty

normally. The rationale of this approach is not validated by controlled studies, but mainly derived from an empirical approach.

Meals with low-fat content and with low residue should be recommended for gastroparesis patients, since both fat and fiber tend to delay gastric emptying. Small meal size is advisable because the stomach may only empty an ~ 1 – 2 kcal/ min. Therefore, small, low-fat, low-fiber meals, 4 – 5 times a day, are appropriate for patients with gastroparesis. Increasing the liquid nutrient component of a meal should be advocated, as gastric emptying of liquids is often normal in patients with delayed emptying for solids. [38,43] Poor tolerance of a liquid diet is predictive of poor outcome with oral nutrition.[43] High calorie liquids in small volumes can deliver energy and nutrients without exacerbating symptoms.

For patients with gastroparesis who are unable to maintain nutrition with oral intake, a feeding jejunostomy tube, which bypasses the affected stomach, can improve symptoms and reduce hospitalizations.[85] Placement of a jejunal feeding tube, if needed for alimentation, should be preceded by a successful trial of nasojejunal feeding. Occasionally, small bowel dysfunction may occur in patients with gastroparesis leading to intolerance to jejunal feeding.

Enteral feeding is preferred over parenteral nutrition for a wide range of practical reasons, such as costs, potential for complications, and ease of delivery.

2.10.3 Gastric neuromodulation

GNM is achieved by delivering low-energy, high-frequency electrical stimulation (about four times that of the stomach basal rate) to the lower part of the stomach via an implantable system. Although the exact mechanism of the action is unknown, the possible explanations for efficacy of GNM are following:

- increase in GE.
- enhancement of fundus relaxation (accommodation).
- decrease in gastric sensitivity.

- enhancement of postprandial gastric slow-wave amplitude and velocity.
- activation of afferent sensory pathways to central mechanisms for nausea/vomiting control.
- alteration of cholinergic/sympathetic pathways.

The first report of gastric pacing (high-energy, low-frequency stimulation) was published in the 1960s. GNM with Enterra (Medtronic device) has been available in Europe since 2002.

Hypothesis: GNM is effective for drug refractory gastroparesis patients and it is safe and effective on long-term use.

Procedure: The Enterra GNM system consists of implantable components (two intramuscular electrodes and a battery-powered neuromodulator, called an IPG (Implantable Pulse Generator) and a non-implantable physician programmer

The system can be implanted through laparotomy or laparoscopy – the decision depends on the clinician's choice and the patient's past medical history. Post surgical gastroparesis patients would generally need laparotomy for electrode implantation where as diabetic gastroparesis or idiopathic gastroparesis patients would be suitable for laparoscopy. The implantation is performed under general anaesthesia and can take around one hour. The two electrodes are fixed to the muscle layer of the greater curvature of the gastric antrum approximately 10 cm proximal to the pylorus and 1 cm away from each other, using non-absorbable polypropylene suture. They are connected to the IPG, which is placed in a subcutaneous pocket in the abdominal wall (typically the upper left quadrant). Following the implantation and patient's recovery, the system is switched on. The rate and amplitude of the current can be non-invasively adjusted to optimize treatment for each patient.

- There is conflicting data about the effectiveness of GNM
- In 2003 a blinded randomised controlled study, 33 patients (17 diabetic, 16 idiopathic) underwent a one-month, blinded crossover condition whereby

they experienced a one-month ON period followed by a one-month OFF period. The crossover period (phase I) was followed by a 12-month open-label phase with regular follow-ups (phase II). In phase I, significant improvement in median vomiting frequency was found in the ON period in the combined (all patients) group, although the same measure in specific patient groups (diabetic and idiopathic) did not alter significantly between conditions. Patient preference for ON treatment compared to OFF treatment was significant in the combined and idiopathic groups, but not the diabetic patients. At 12 months, weekly vomiting frequency had decreased by over 60% in both groups of patients, with a greater than 80% reduction seen in half of the patients involved in the study. Abell et al[56]

- In the second blinded crossover randomised study, 55 diabetic patients inserted with GNM, reported significant improvements in symptom reporting following the surgery. Patients underwent randomised 3-month ON or OFF period, followed by 3 months of the reverse condition. This was concluded with 4.5 months of ON condition up to a 12-month follow-up. There were no significant improvements shown in the initial crossover period. However, by 12 months Weekly Vomiting Frequency had significantly declined from a mean of 19.5 to just 4.25 episodes per week (a 78% reduction, $p < 0.005$), while Total Symptom Scores (TSS) were reduced in terms of frequency and severity by 35% and 37%, respectively. McCallum et al.[66]

- GNM reduces the use of prokinetic and antiemetic ,27 patients (out of 35) were, at least, on one prokinetic at baseline and 14 of these 29 patients were off prokinetic after 3 years of GES. Similarly, 25 of these 35 patients requiring, at least, one antiemetic (10 patients on two antiemetic and two on three) at baseline decreased to 19 (one on three antiemetic).[89]
- GNM therapy is superior to drugs in improving GI symptoms, healthcare resources and long-term healthcare benefits. [90]
- GNM therapy produces significant improvement in patients' nutritional status (increased body weight and BMI) and reduces the need for nutritional support. [5, 86,92, 93, 105]

GNM with Enterra device is completely reversible, and it can be safely explanted in case of local complication such as infection.

Symptom relief: Reported symptom improvement following GNM therapy (reduction in nausea, vomiting or total symptom score) is greater than 50% in almost 80% of patients.[85,86,87,91,93,96] In some studies, the improvement, was as high as 90%. [91]

Reduction in hospitalisation: In a study of 37 patients, Lin et al [92] showed that hospitalisation days decreased from 50 days to 14 days at one-year post-implantation with 29% of patients requiring no admission, and further decreased to 6 days in three years with 69% of patients requiring no admission. The major reasons for hospitalisation prior to the GNM were complications of gastroparesis.

In a study of 18 patients (9 patients on drug therapy and 9 patients on GES therapy), Cutts et al[52] showed that GNM significantly reduce hospital days, with a decrease from a baseline means of 36.4 to 2.76 days per year at the end of 36 months [182]

In a study of 16 patients, McCallum et al[88] showed that hospitalisation for gastroparesis symptoms decreased from 31 days during the year before receiving GNM to 6 during the first year after GNM, 8 patients (50%) required no hospital admissions.

In a study of 55 patients, Forster et al [85,86] showed that days spent on hospital admissions were significantly decreased. For the year prior to the placement of the GNM, the average for days spent in the hospital was 57 and this fell to 17 the next year. This reduction alone could explain patient's improvement in their QOL.

Reduction in nutritional support and weight gain: Lin et al [87, 88] showed that the need for nutritional support decreased from 15 patients (out of 37) at the baseline to 8 patients at one year after GNM and to 5 patients at 3 years.

Moreover, the median body weight significantly increased at 12 months and was maintained beyond 3 years of GES.

McCallum et al [88] showed that at the time of GNM, 7 out of 16 patients required nutritional support in the form of a feeding jejunostomy but out of these 7 patients, 4 were able to discontinue the jejunal feeding at 2, 4, 6 and 11 months after GNM, and 3 still required supplemental feeding at 12 months. They also showed that average body weight increased by more than 3 kg at six months and continued at 12 months.

Forster et al [47, 49] showed that BMI and body weight increased significantly. In terms of nutritional parameters, the patients' average body weight increased by almost a kilogramme and the BMI by 0.4 units. The majority of patients had their jejunal feeding tubes removed by one year and no one was receiving TPN. Of the 25 patients who had a jejunal feeding tube after GNM, only 8 (32%) required this feeding approach at 12 months.

Diabetic gastroparesis patients may lead to caloric and electrolyte deficiencies as well as significant weight loss. Two patients deemed unacceptable candidates for renal transplantation because of marked malnourishment and a concern that they would not be able to tolerate immunosuppressant medications. In less than two years following GNM, two patients underwent a successful kidney transplant.[101]
Anand et al [95] showed that the survival rate was lower for diabetic patients not implanted with GNM than the survival rate of diabetic patients implanted with GNM

GNM is a viable treatment option for the patients suffering from chronic nausea and vomiting (secondary to gastroparesis) for whom conservative therapy has failed and who do not want to undergo surgery.

3. **Capsule endoscopy as a tool to assess GI motility**

3.1 Introduction

The small intestine is difficult area to assess because of the distance from the mouth. The mainstay of investigations for the small bowel has been radiological investigations, barium contrast studies, CT scan, scintigraphy and MRI. Although there are certain advantages of CT scan and MRI, small and flat lesions within small intestinal wall may be missed by these modalities. Double balloon enteroscope can be used to investigate and treat small and flat lesions within small intestine but it is time consuming and generally uncomfortable for patients.

Capsule endoscopy (CE) emerged as an option to diagnose small intestinal problems in 2001.[95] Technology has improved since then and now high-resolution video of the small intestine is possible with capsule endoscopy without the need for sedation or radiation.

Indications of capsule endoscopy.

Obscure GI bleeding is the primary indication for CE. 70–80% patients undergo CE for this indication,[96] and two recent meta-analyses have shown that CE is better in diagnosing obscure GI bleeding compared to radiological investigations and that it is safer than push endoscopy.[95,96] On the basis of a large amount of published data, it is now considered a valuable tool to diagnose obscure GI bleeding.

The incidence of small intestinal Crohn's disease is about 45% of the total number of patients with Crohn's and in 25% it is confined to the terminal ileum.[99] The diagnostic yield of CE in Crohn's disease of small bowel is between 30–70%.[95, 96] There is a theoretical risk of capsule retention in patients with Crohn's disease; however, this risk was not more than in patients with obscure GI bleeding.[100] The risk of capsule retention in patients with diagnosed Crohn's stricture is high (5–13%). [94, 101] CE is therefore considered an important tool in diagnostic work-up in patients suspected of Crohn's disease.

Other indications for the use of CE include non-steroidal anti-inflammatory drugs (NSAID-induced small ulcerations, and erosions in the stomach and the intestine. Although traditional endoscopy and biopsy remains the gold standard for the diagnosis of celiac disease, some authors have noticed significant positive and negative predictive values of CE in these patients.[92.93] Small intestinal tumors account for 1–2% of primary GI tumours. The rateof capsule retention in larger-size tumours will be relatively high; however, these patients will subsequently require surgical resection decreasing the risk of the capsule being left in the small intestine. CE is also used in a limited number of patients with abdominal pain. Two studies used CE in such patients after extensive diagnostic workups and did not find any significant pathology in 85% of cases.[94.95]

Current British Society of Gastroenterology (BSG) guidelines on the role of CE:[77]

1. Second look upper GI endoscopy before CE in patients with high suspicion of upper GI bleeding.
2. An upper and lower GI endoscopy should be performed for obscure GI bleed before CE.
3. Patients should be counselled and the risk of capsule retention should be explained.
4. The CE should be kept for patients with undiagnosed obscure GI bleeding.
5. Patients with high suspicion of small bowel Crohn's should be considered for CE.
6. There is a role of CE in refractory celiac disease and its associated complications.

AIM:

The review of the published literature and the BSG guidelines elaborate the role of CE in obscure GI bleeding, Crohn's disease and small intestinal tumours. This is, however, dependent upon its transit through the GI tract, and subsequently dependent upon GI motility. The role of CE in assessing GI transit

is not very well established and we, therefore, conducted a retrospective study to elaborate its role in the assessment of GI motility.

3.2 Methodology

A total of 113 patients underwent CE in two regional (East Yorkshire) centres from 2006 to 2010. The centers included:

1. Hull and East Yorkshire Hospital NHS Trust
2. Scarborough Hospital NHS Trust.

The number of capsule endoscopy/centers:

Hull (June 2006–June 2010) = 70

Scarborough (Aug 2007–Dec 2009) = 43

3.3 Patient preparation and procedure:

Patients were instructed to continue a normal diet up to one day before CE. They were advised to stay on tea, coffee, juice and clear fluids in the evening before CE and not to eat and drink anything after midnight. Bowel preparation was not used routinely in these patients. Patients were also suggested to continue their medications (except prokenitics) on the morning of the test. They were advised to wear loose clothes and attend the CE suite in these centers. They were seen by the CE specialist nurse and informed consent was taken. Small adhesive pads were applied to the abdomen and data recorders were attached (Figure 4). Patients were then advised to swallow the capsule with sips of water. They were advised not to eat and drink anything for two hours, with only clear fluid after two hours, and were allowed to have a light snack after four hours. They were free to walk around or stay in the CE unit and they were also authorized to go home and come back after eight hours. Waist belts and data recorders were retrieved and video data later was reviewed by clinicians.

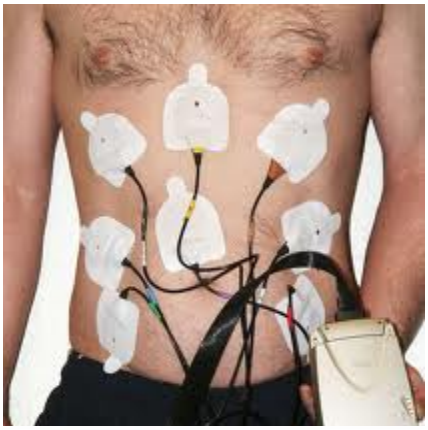


Figure -5: Components and methodology of CE

Leads, data recorder, equipment and CE

3.4 Data collection:

Clinical reports of CE were generated by consultant physicians. Patient data (video, letters, notes) was revisited by the researcher for the assessment of GI motility. The following additional information along with the demographic data was recorded.

1. Time of capsule ingestion
2. First image of stomach and time of this image
3. First image of D1 (first part of the duodenum) and time of this image
4. Identification of caecum and time

GE time was calculated from the time taken from the first image of the stomach to the first image of the duodenum. This was also confirmed by the data of the capsule journey in the GI tract. (See Figure 5, the capsule journey in the stomach is marked with a blue line.)

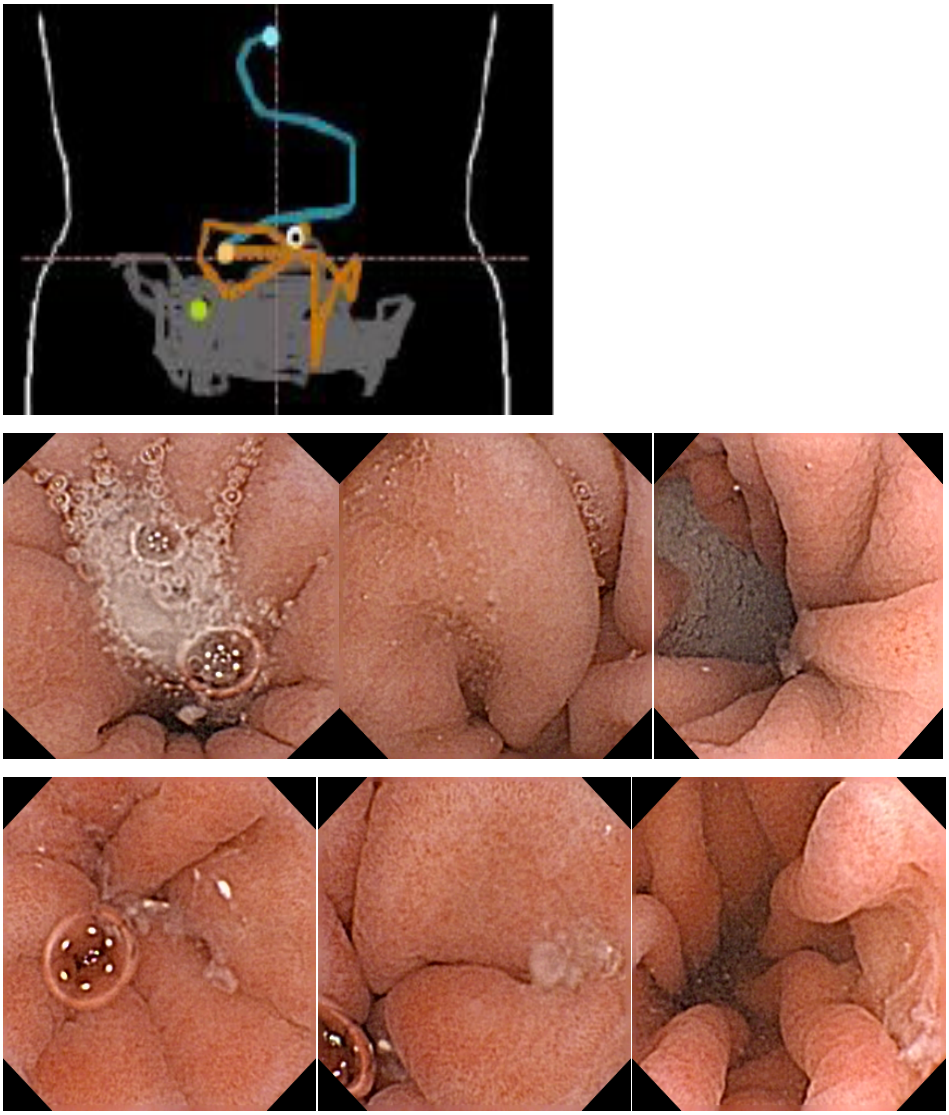
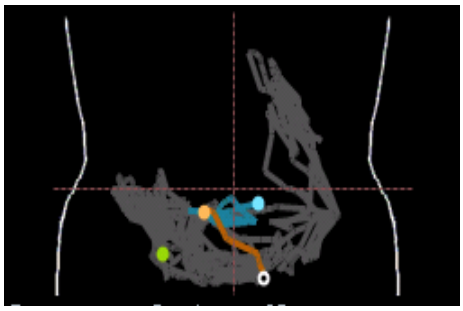


Figure -6: Capsule journey and GE

The journey of the capsule in the stomach marked in blue and pictures taken during its journey in the stomach.

Intestinal Transit Time: Calculated by the time taken by the capsule from D1 to the caecum (Figure 6).



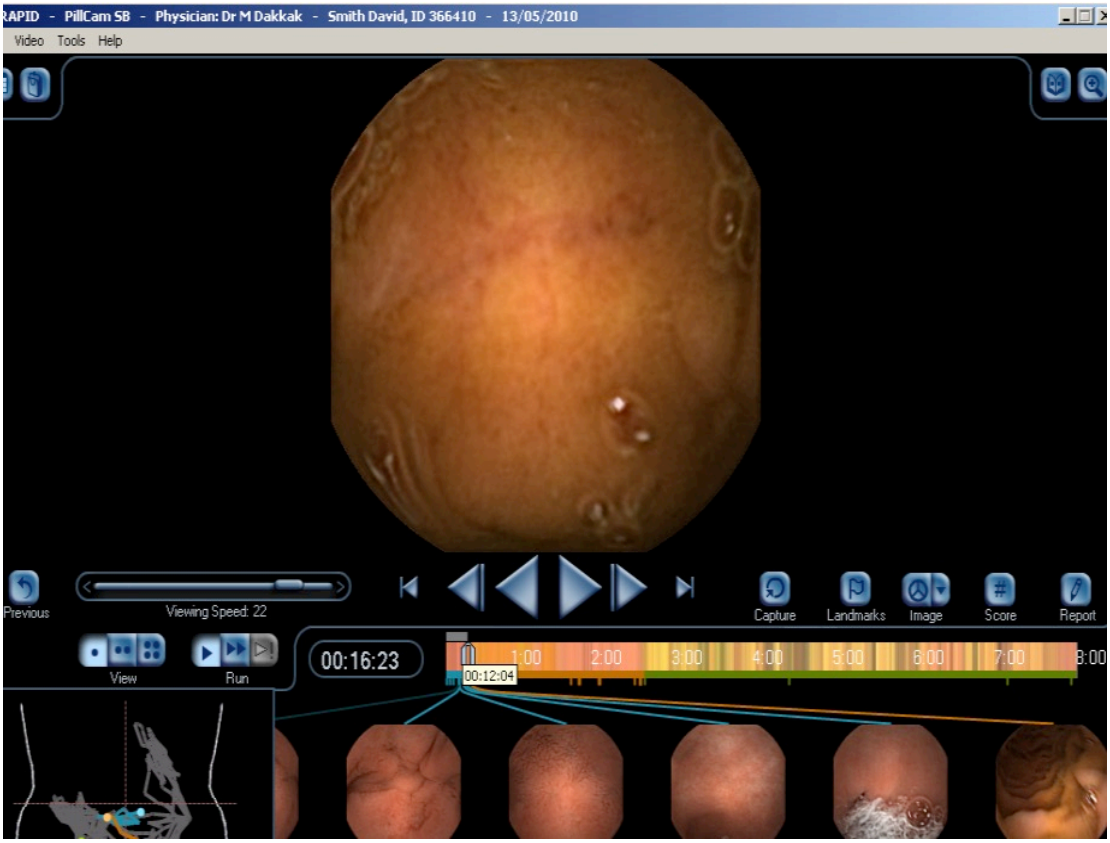
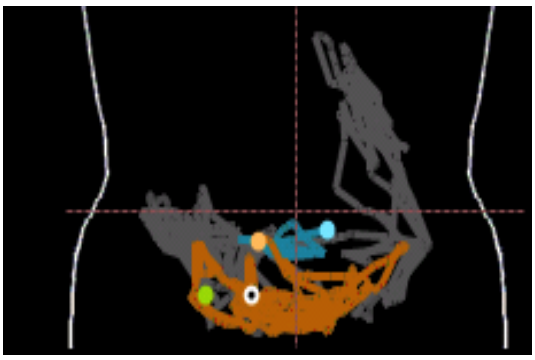


Figure 6: Capsule journey in the duodenum

Figure 7: Capsule journey marked with brown colour in the duodenum. And the figure below showing the images of the distal stomach and first duodenal image when the capsule enters the duodenum.



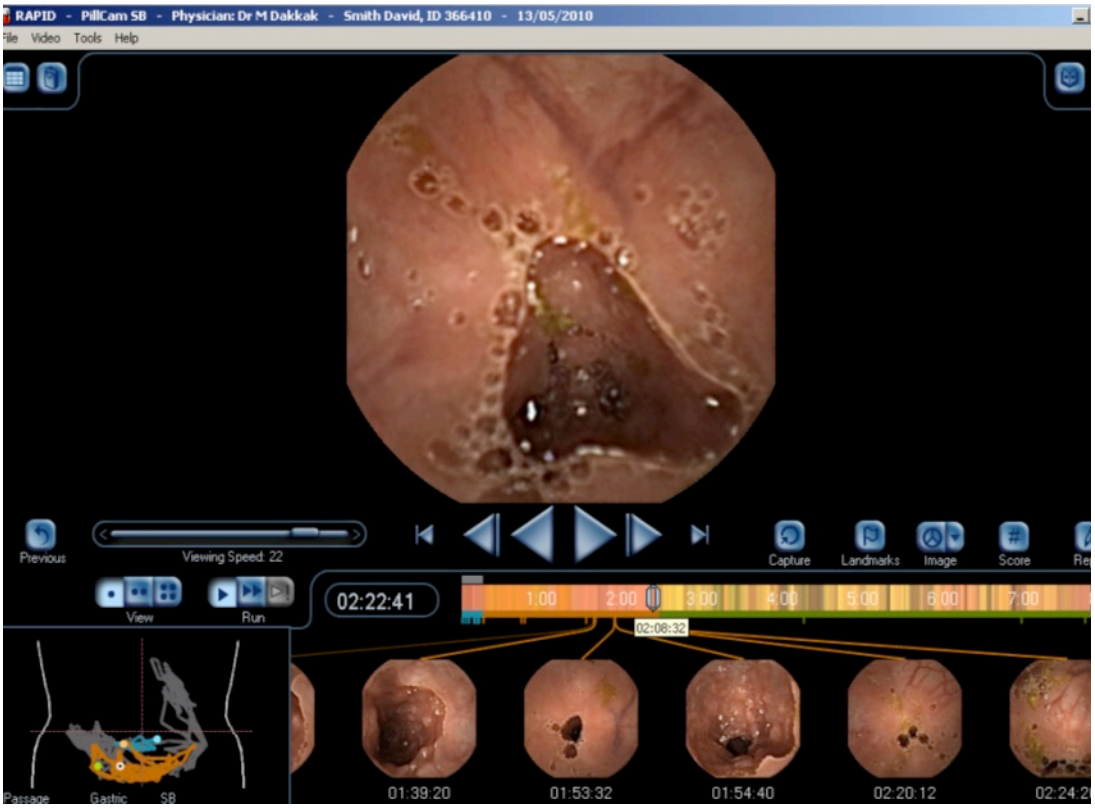
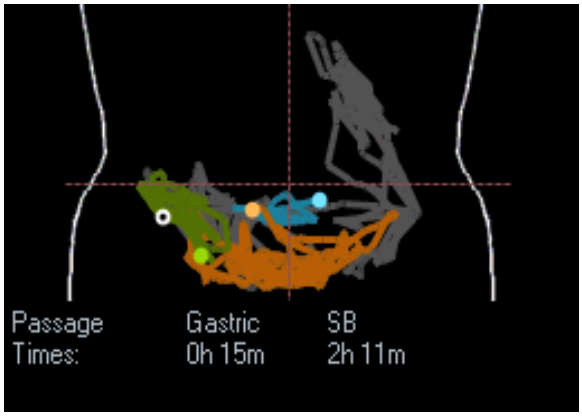


Figure 8: Capsule transit through the small intestine

Figure 7: Capsule journey marked in brown in the small intestine. The second image demonstrates pictures taken in different parts of the ileum, until the capsule is seen in the terminal ileum at 02:22:41 after ingestion. Time of entry in the duodenum is subtracted from the total time to calculate IT.



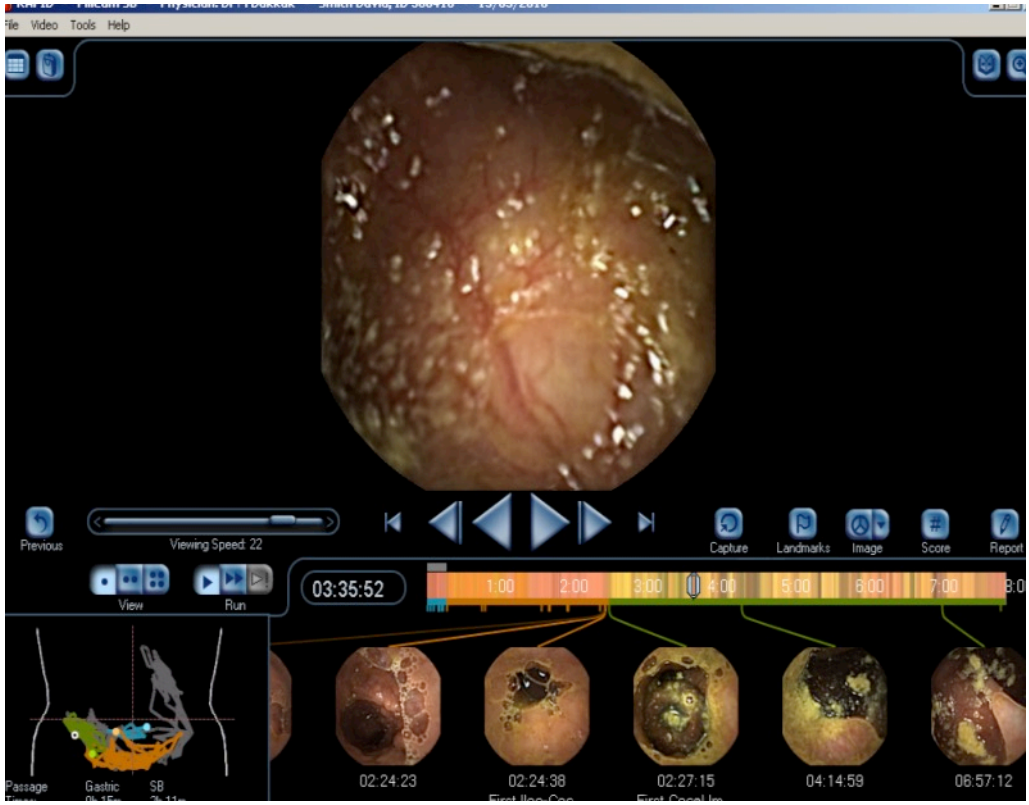


Figure 9: Capsule transit through the terminal ileum and into the caecum

Figure 8: These figures demonstrate the journey of the capsule in the terminal ileum and caecum. Images taken at 02:24:38 demonstrate the ileocaecal valve. The capsule entered the caecum at 02:27:15 as shown in the images above. The capsule continued to move in the caecum thereafter, as shown in the capsule journey (colour green) in both images.

Identification of the caecum can sometimes be difficult in CE. However, the change in villous pattern and identification of the ileocaecal valve along with identification of caecal landmarks help to identify the caecum. Figure 9 demonstrates the presence of submucosal blood vessels, semisolid faecal matter and loss of the villous pattern of the ileum.

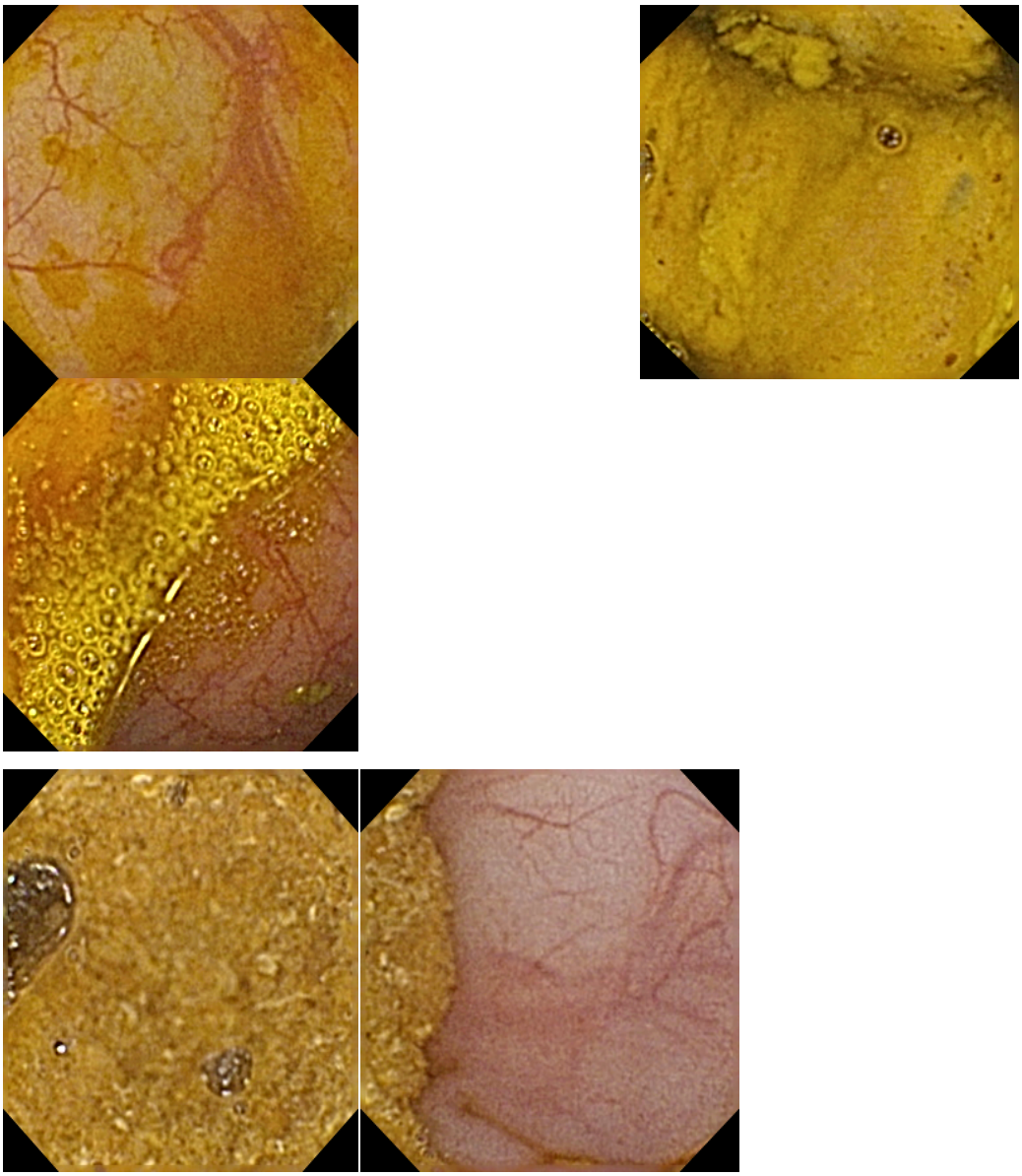


Figure 10: Identification of the caecum:

3.5 Study approval

Study approval by the hospital clinical governance department was obtained. Video, electronic and paper records were reviewed in this study.

3.6 Statistics

Data was entered into an Excel datasheet and statistical analysis was performed using SPSS 17. Values are expressed as mean +/- standard deviation (SD) unless otherwise stated. The significance of difference was calculated using two-tailed paired or unpaired Student t tests.

3.7 Results

A total of 113 patients underwent CE during this period. The male to female ratio was male 61 (54%): female 52 (46%). The mean age of the patients was 56+/-17 years (range 17–84 years). ASA grade included 1 = 15 (13%), 2 = 68 (61%), 3 = 29 (25.5%), 4 = 01 (0.5%).

Indications for capsule endoscopy are explained in Table 3-1. The majority (84%) of these patients underwent CE as a part of the diagnostic process for anemia of unknown origin/occult GI bleeding. 6 patients (5%) had a known source of GI bleeding and were further assessed by CE. Other causes included suspected or part of a workup for inflammatory bowel disease in seven patients (6.1%) and rare indications included abdominal pain in three patients, and weight loss investigations in one patient.

Findings of CE are explained in 3-2. CE was reported to be normal in 23 cases (20%). Areas of redness or red spots of unknown origin were found in 14 patients (12%). Small bowel erosions were seen in 10 patients (8%), ulcers in the small intestine in 9 patients (7.5%) and polyps in the small intestine in 8 patients (7%). Bleeding sites were identified in the small intestine in 3 patients and stomach in 2 patients. Crohn's workup/evaluation was carried out in 2 patients. Angiodysplasia and telangiectasia were seen in 12 patients (10%).

Collectively, the findings were picked up in 68 cases (60%). In one patient, threadworms were identified as a cause of symptoms. Some of these findings are presented in the tables below.

Table 3-1: Indications of CE

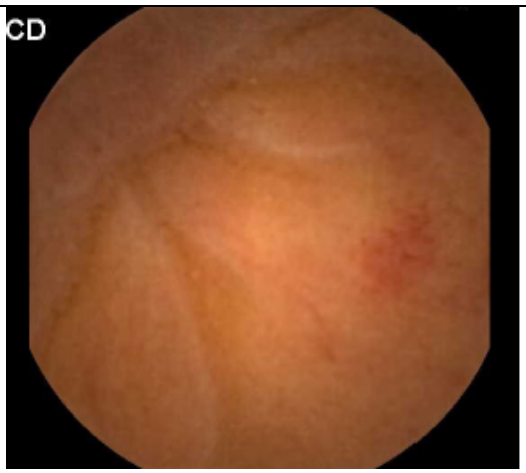
Indications	N	%
Anaemia	96/113	84
Bleeding	6/113	5.3
Weight loss	1/113	0.88
Inflammatory bowel disease	7/113	6.1
Abdominal pain	3/113	2.6

Table 3-2: Findings of CE

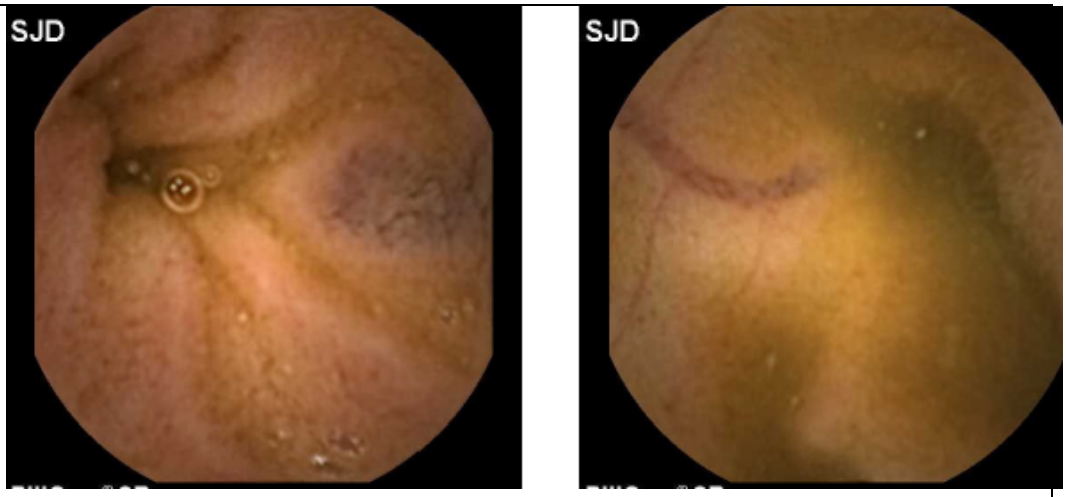
Findings	**N**
Angiodysplasia	6
Ulcers (stomach) +/- bleeding	2
Ulcers (small bowel)	9
Erosions (stomach)	5
Erosions (small bowel)	10
Polyps in small bowel	8
Crohn's disease	2
Red spots/area of redness	14

Bleeding site (small bowel)	3
Threadworm (small bowel)	1
Telangiectasia	6
Bowel narrowing	2
Total	68 (60%)
23/113 (20%) normal	

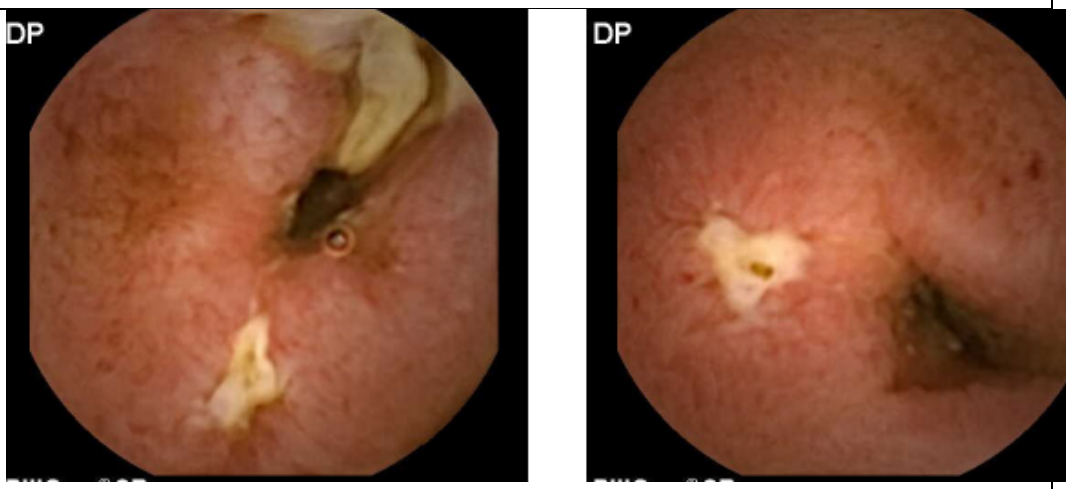
Threadworm

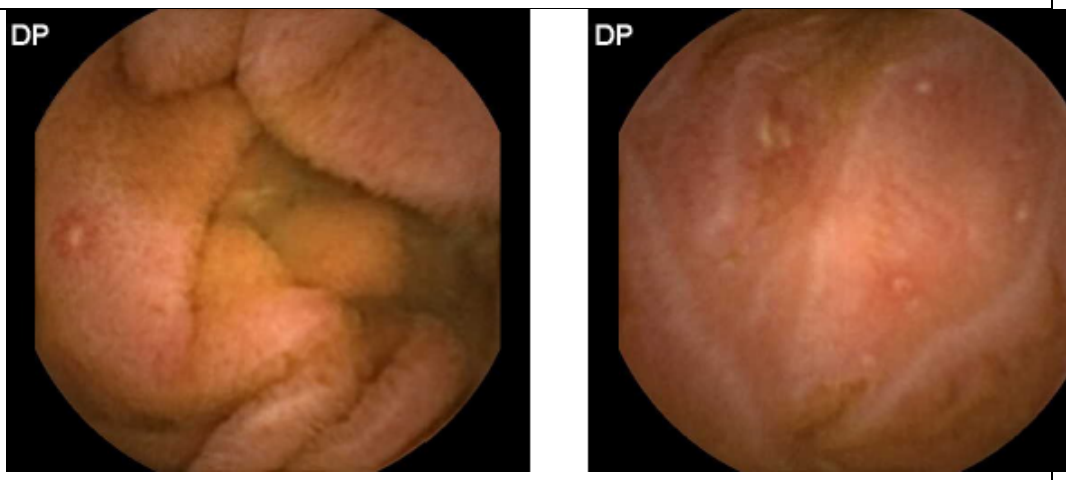


Angiodysplasia of the jejunum

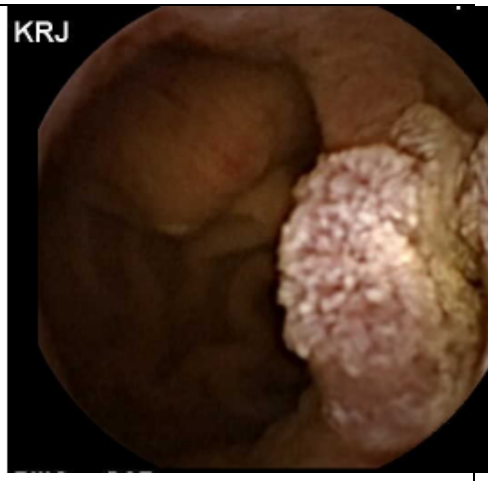


Angiodysplasia of the jejunum

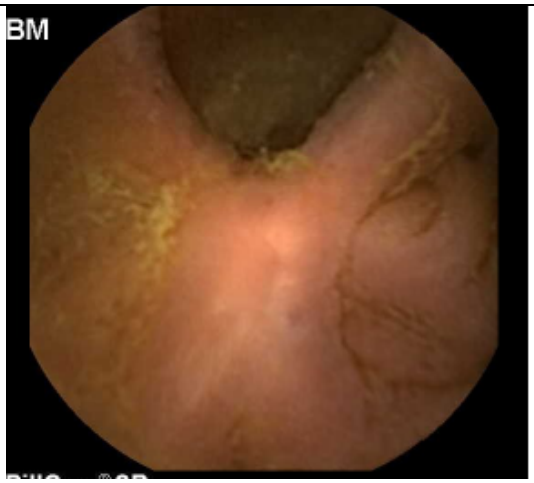


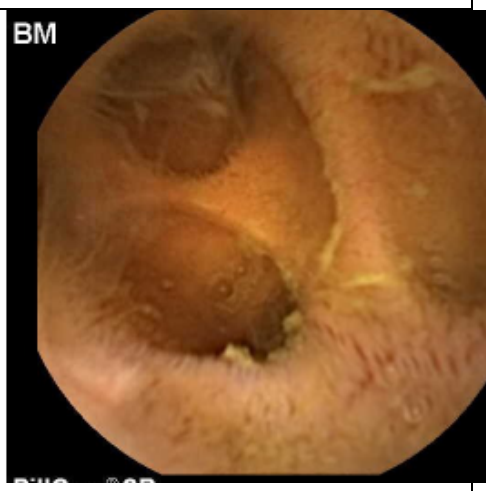


Aphthous ulcers in the jejunum and ileum

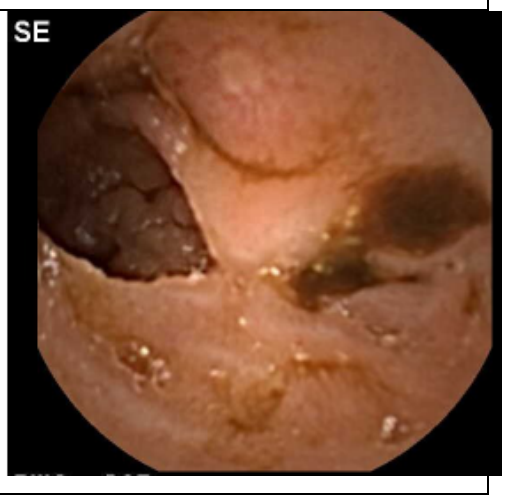


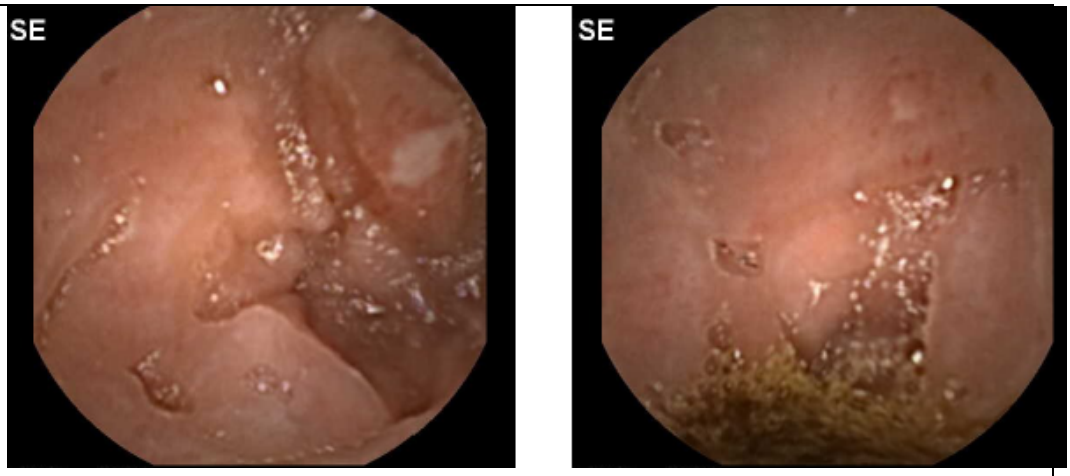
Duodenal and early jejunal polyps





Diverticuli in the jejunum and ileum





Ulcers in the distal ileum; thick oedematous mucosa – suspected Crohn's disease

Figure -11: Pathologies identified with CE

Mean capsule passage time in the stomach was 00:31 (SD 39) minutes (median 00:17, range 01:00-05:00). Similarly, mean capsule transit time in the small intestine was 04:40 (SD 01:20) hours (median 04:22, range 01:02-07:44) (for details see Table 3-3) The capsule failed to reach the caecum in 8 patients (7%). This included 2 post-surgical (Crohn's disease) patients, 1 with DM, whereas no apparent cause was seen in 5 patients. The capsule reached the caecum after > 6 hrs in 22 pts, > 7 hr in 3 pts. Capsule retention in the stomach was observed in 3 patients, including 1 post-procto-colectomy and 2 unknown causes.

A subgroup analysis of 12 patients with long-standing DM revealed gastric passage time of 00:45 (SD 122) minutes and intestinal passage time of 05:31 (SD 02:03) hours. These patients matched for age and American Society of Anesthesiologists (ASA) with the non-DM group. Comparison of the DM group with the rest of the patients did not show any significant difference in gastric passage time; however, intestinal passage time was significantly prolonged in the DM group (p-value 0.07, 0.004 respectively) (Table 3-4).

Opiates or opiates derivative use was observed in 4 patients. The mean age of this group was 52 years. Gastric passage time was 00:50 (SD 00:55) and intestinal passage time was 04:14 (SD 01:38) hours. This difference was not

statistically significant compared to patients not on opiate analgesia (p 0.36, p 0.29 respectively).

2 out of the 113 patients required repeat CE (1 could not swallow, 1 had inadequate bowel preparation). 1 patient experienced nausea 14 days after CE and an X-ray of the abdomen revealed a capsule in the small intestine. Symptoms, however, settled spontaneously and the patient did not require surgery. No other complications were observed in this group of patients.

Table 3-3: GE and IT passage time of CE

	Minimum	**Maximum**	**Mean & SD (Hr: Min)**	**Median**
Gastric passage time (N=110)	00:01	05:00	00:31 (39)	17
Intestinal passage/transit time (N=95)	01:02	07:44	04:40(01:20)	04:22

Table 3-4: Capsule passage time in diabetic patients

	Minimum	**Maximum**	**Mean & SD (Hr: Min)**	**P**
Gastric passage time	00:02	05:00	00:45 (1:22)	0.07
Intestinal passage/transit time	02:59	08:18	05:31(02:03)	0.004

3.8 Discussion

The British Society of Gastroenterology (BSG) has issued guidelines elaborating the role of CE, and these were published in 2008.[98] CE uses a 26x11 mm disposable capsule containing a battery, camera, image transmitter, antenna and a light source (Figure - 4). The capsule travels with GI motility. There are three major companies manufacturing CE: Pillcam SB by Given Imaging Ltd, Endocapsule by Olympus and OMOM capsule by Jinshan Science and Technology Group.[98] One of our centres used Pillcam and the other used Endocapsule. The equipment and techniques are similar to both companies. The approximate battery life is 8 hours, and previous literature has demonstrated that in 85% of cases the capsule can reach the caecum by this time. In this period, CE records approximately 50,000 images. The main limitations of CE include inadequate bowel preparation and incomplete examination because of limited (8 hours) battery time, and slow transit of the capsule through the GI tract. Based upon these limitations, CE completion rate is published between at 75–90% of different pathologies.[84,93, 96] In a recent meta-analysis, the diagnostic yield of CE in diagnosing occult GI bleeding was reported to be better than other modalities[96] When comparing CE with other forms of endoscopy (enteroscopy), the diagnostic yield was similar.[86,96] Diagnosis of small intestinal Crohn's disease is difficult and previous studies have compared the other modalities with CE. 45% detection of Crohn's disease has been reported in a recent meta-analysis.[96] In another study, the yield for CE versus ileoscopy was 61% and 46% respectively, showing CE as a better tool for investigation of small intestinal Crohn's.[95] The main complication of CE is capsule retention. It is, therefore, important that patients should be fully informed about the procedure. Variable results of capsule retention have been reported from 0% (healthy subjects) to 21% (intestinal obstruction).[94] This problem may be more common in patients with Crohn's disease as there is a high risk of ulceration and stricture formation in Crohn's disease. False negative results are reported to be around 11% (range 5–18%) because CE may miss some information.[97] Other limitations include the inability to control the movement, transit through the GI tract and biopsies cannot be taken. The findings were in line with the published data, indicating total finding pick-up rate of 60% and normal CE in 20% of

cases. In the rest of the patients, findings were considered not suggestive of any firm conclusions. The capsule failed to reach the caecum (incomplete CE) in 7% of cases.

GI motility depends on multiple factors, including the food composition, medications and body fluids. The results of gastric passage time and intestinal transit (IT) time in this study were comparable to a large published study to assess GE and intestinal transit (IT) using CE.[98] This study published the GI motility data of 790 patients using CE and reported GE time of 0:41 ± 0:49 and intestinal transit (IT) time of 4:22 ± 1:30 hours in subjects over 40 years of age. There was no significant difference in GE time; however, intestinal transit (IT) time was prolonged in the >40 years age group. A subgroup analysis of health volunteers revealed GE time of 0:39 ± 0:43 and intestinal transit (IT) time of 3:56 ± 1:22 in 87 subjects. GI motility results are comparable between healthy subjects and patients with celiac disease, obscure GI bleeding, PAF (familial adenomatous polyposis), intestinal lymphoma and ulcerative colitis. In this study, gastric passage time was 00:31+/-00:39 minutes which demonstrates fast GE comparable with this published data.[98] In addition, we noticed a wide range of our gastric passage time data (range 01:00-05:00) and in 3 patients the capsule failed to leave the stomach without any obvious reason. In patients with very short gastric passage time, the capsule fell into the pylorus and passed quickly into the duodenum. This cannot be representative of true GE in these patients.

However, mean capsule transit time in the small intestine (04:40+/-01:20 hours) was comparable with the largest published study[98] suggesting that the assessment of intestinal transit (IT) may be more reliable using CE. In our experience, the gastric passage time in patients with DM was unaffected; however, intestinal transit (IT) time was significantly prolonged in those patients (Table 3-4). There is no published available data to compare this finding. Besides, we noticed that gastric passage time was prolonged in patients with opiate use, but their results should be cited with caution as the number was very low (n=4).

In 1 of our patients, there was severe oesophageal spasm and the capsule failed to progress three hours after ingestion Figure -8 (pictures taken after every 30 minutes). In another patient, the capsule was retained in the stomach. This patient was suspected of Crohn's disease and subacute bowel obstruction. Food and bile were visible in the stomach, and the capsule remained in the stomach during the study time. The patient later underwent small bowel resection for a terminal ileum stricture. The capsule passed spontaneously through the small intestine after the operation. Some unusual findings like diverticuli of the small intestine and ringworm were also identified.

Limitations of CE.

Battery life is approximately 8 hours. In some cases, the capsule may not reach the caecum during this time, and therefore, the test will be classified as incomplete. In our study, the capsule failed to reach the caecum in 8 cases (7%). This represents slow GI transit as no other cause of obstruction was identified.

Another limitation of CE is the inability to take a biopsy of lesions found in the small intestine. This may necessitate enteroscopy in such patients; however, this may also fail to obtain biopsy or resection subject to the distance and length of scope, technical inability and patient factors.

Inability to manoeuvre the capsule may result in missing some part of the mucosa. Based upon the previous studies, 10–15% missed mucosa was reported. This may result in missing some important information which may lead to false negative results.

Bowel preparation can hamper the image quality and, therefore, lead to incomplete tests or inaccurate results. This can be rectified by bowel preparation and a repeat examination. In our study, two patients required a repeat test on these grounds.

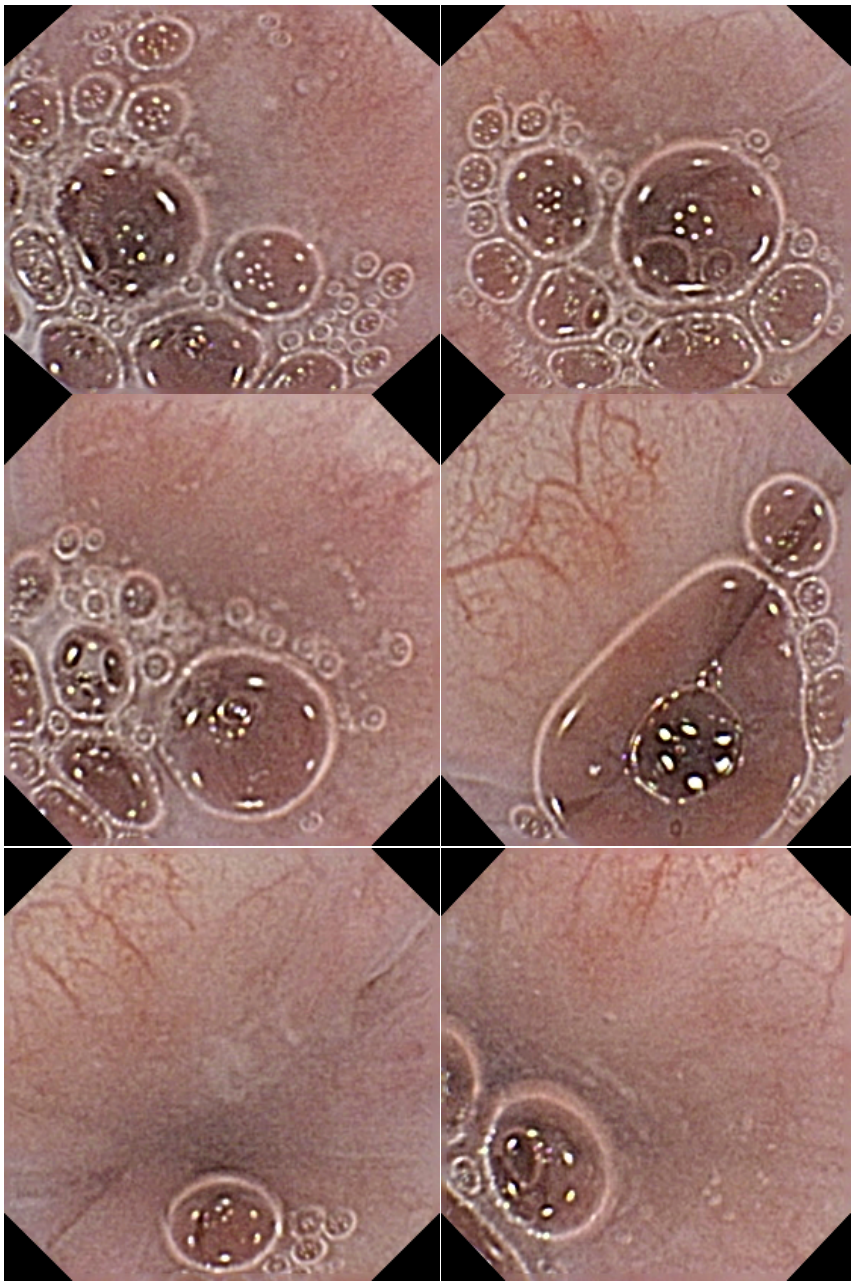


Figure -12: Oesophageal sphincter spasm

Oesophageal sphincter spasm. Capsule failed to progress until 3 hours after ingestion. Six pictures were taken at 30-minute intervals.

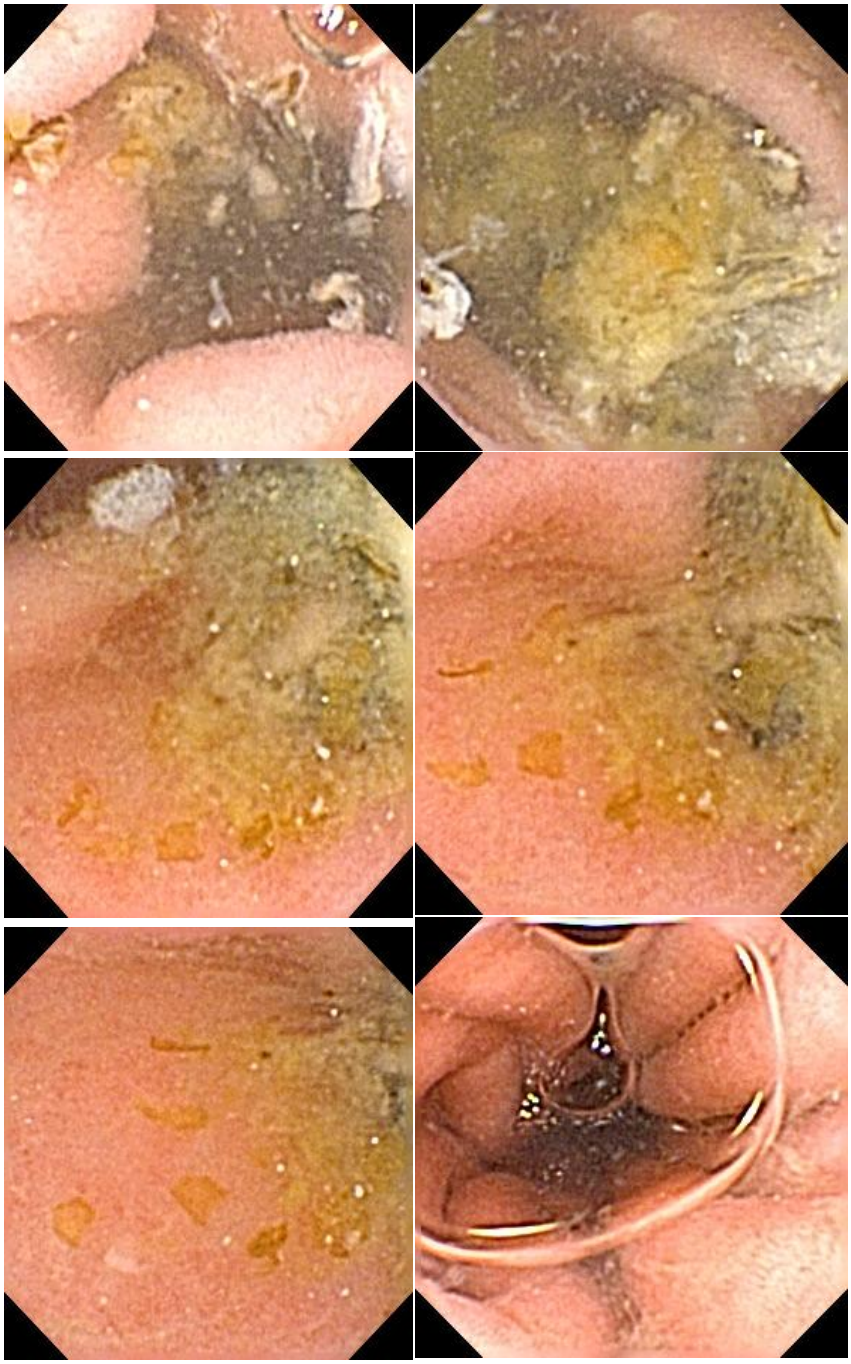


Figure -13: Crohn's stricture on CE

A patient with Crohn's stricture and subacute small bowel obstruction. Food and bile is visible in the stomach. The capsule failed to progress in the small intestine and was retained in the stomach.

3.9 Conclusion:

The role of CE is well established in obscure GI bleeding. It is also a valuable tool in the assessment of Crohn's disease, celiac disease and other small bowel pathologies. We propose that it can be used as a tool to assess intestinal transit. It may not be a true representative of GE.

4 Efficacy of Temporary Gastric Neuromodulation

Excerpts of this chapter have been modified and presented at European society of surgical research, ESSR 2013

Akbar MJ, Ullah S, Mehmood S, MacFie J. Gastric neuromodulation for drug refractory gastroparesis, and persistent nausea and vomiting. (ESSR 2013).

4.1 Background

Gastroparesis is a chronic disorder of the stomach. The delayed GE of a solid meal defines it, in the absence of mechanical obstruction. It is a debilitating condition. Gastroparesis patients have poor oral intake, it can develop complications, such as electrolyte imbalance, dehydration and malnutrition.

The gastroparesis symptoms are non-specific and include nausea, vomiting, abdominal distension, early satiety and abdominal pain. [61,82] These symptoms can mimic multiple illnesses including gastric ulcers, gastric outlet obstruction, biliopancreatic disorders, gastric cancers and bowel pathologies.[62] Therefore, it is diagnosed after the exclusion of other organic gastric pathologies and confirmed with objective evidence of delayed gastric emptying (GE). Gastroparesis can be primary (idiopathic) up to one-third of patients or secondary in two third of patient. Secondary gastroparesis is due to conditions such as diabetes Mellitus, postsurgical . Almost half of secondary gastroparesis are due to Diabetes mellitus, and remaining half are post-surgical (ie post gastric surgery and vagotomy)

The treatment modalities for gastroparesis include the treatment of underlying cause, dietary adjustment, and antiemetic and prokinetic medications. Gastric neuromodulation (GNM) has evolved as a new treatment option for severe and drug-resistant gastroparesis over the last decade. The GNM is expensive ((£10500) it requires general anaesthesia and commonly laparoscopic procedure to implant GNM device into the abdominal wall. However, there is conflicting data available on the effectiveness of GNM as discussed in chapter 2.

This study was designed to assess the suitability of GNM for gastroparesis patients by avoiding the risks of GA and surgery as well as expensive enterra device. We focused on multiple criteria to assess overall patient response. It included symptomatic assessment, nutritional outcome in terms of weight gain, assessment of quality of life using validated short form survey version 2 (SF12 V2) and objective measurement of half gastric emptying time with gastric scintigraphy during the trial period of seven days for each patient.

4.2 Methods

4.2.1 Patient selection and assessment

Patients with symptoms of gastroparesis who failed to respond to medical treatment and who were not found to have any correctable pathology were selected for consideration of temporary GNM. At least one of the two symptoms (Nausea and/or vomiting) had to be severe (if associated with malnutrition or impairment of quality of life) then patient was included for the procedure. The patients were investigated to exclude mechanical gastric outlet and bowel obstruction by endoscopy and radiological investigations including plain abdominal radiograph, CT scan and contrast studies. All patients had an initial trial of antiemetic and/or prokinetic drugs for at least six months. After failure with medical treatment, they were considered for a trial of temporary GNM. Baseline data such as gastroparesis symptom score (GSS), vomiting frequency score (VFS), quality of life using short form survey version 2 (SF12 V2) and nutritional status were assessed (using daily caloric intake, use of supplemental nutrition and body weight) in the selected patients. GSS is the sum of 5 four-point categorical scales (0 for absent up to 4 for extremely frequent and extremely severe) for symptoms such as vomiting, nausea, early satiety, bloating and abdominal pain. Besides, all the patients underwent a standard gastric scintigraphy before GNM.

Detailed descriptions of the clinical problems of these patients are as follows:

Patient 1 GT: This 57-year-old gentleman underwent surgery (gastrojejunostomy) for an annular pancreas in 1998. Later on, he had persistent symptoms necessitating surgeries including Roux-en-Y gastric bypass (RYGB) in 2001 and refashioning in 2004. He had multiple inpatient admissions and outpatient follow-ups for nausea, vomiting, bloating, tiredness and early satiety. He required nutritional support and yet struggled to put on/maintain his weight. He was investigated and confirmed not to have a mechanical obstruction on numerous occasions. He required prokinetics and antiemetics and was unable to eat and drink properly. Pre-operative investigations confirmed delayed gastric half-emptying with a time of 514 minutes. A detailed description of gastric symptom severity score (GSS) is described below (Table 4-1, Table 4-21 and Table 4-22).

Patient 2 DH: A 40-year-old gentleman with long-standing gastrointestinal dysmotility. He underwent an ileostomy in 2005 for intractable slow transit. Ileostomy output reduced over the period and was working only 2–3 times a week. He suffered from nausea, vomiting (20–40 times a week), bloating, early satiety and abdominal pain. He took Domperidone, an antiemetic and Movicol.

His work and social life were significantly limited. He had six admissions to the hospital within a year and was extensively investigated. There was no mechanical obstruction found on CT scan and other contrast studies. Subsequent GE studies revealed prolonged GE, half-emptying time 104 minutes, and he was considered suitable for GNM. Pre-operative GE and GSS are described in Table 4-2, Table 4-21 and Table 4-22 respectively.

Patient 3 CS: This 44-year-old gentleman presented with a long-standing history of nausea, vomiting and weight loss. He had lost 18 kg in weight, and vomiting frequency was at least 20 times a week over the last four years. These symptoms significantly limited his work and social life. He was on

regular antiemetics and prokinetics. He had a CT scan, small bowel studies, oesophageal manometry and gastric scintigraphy. All the investigations were inconclusive and based on the gastric scintigraphy and barium studies he was diagnosed with slow GI transit (gastroparesis). He was therefore considered suitable for GNM. His GE and GSS score are described in Table 4-3, Table 4-21 and Table 4-22 respectively.

Patient 4 SM: This 57-year-old lady was referred with severe nausea, vomiting, bloating, abdominal discomfort and early satiety for the last few years. She had lost weight (4 stone) and appetite and continued to vomit 3–4 times a week. Her past medical history included long-standing DM (15 years), arthritis and depression. Her medications included Metformin, Movicol, Dulcolax, Morphine and antidepressants. She was investigated and confirmed not to have a mechanical bowel obstruction. Pre-operative investigations confirmed delayed gastric half-emptying (time 98 minutes). GE and GSS are described in Table 4-4, Table 4-21 and Table 4-22 respectively.

Patient 5 LP: This 54-year-old lady suffered from intractable nausea, severe bloating, abdominal pain and early satiety in the last few years. Her past medical history included long-standing backache and hypercholesterolemia. Her medications included Tramadol, Simvastatin, Movicol and Paracetamol. She was investigated and confirmed not to have mechanical bowel obstruction on CT scan. Pre-operative investigations revealed the gastric half-emptying time of 37 minutes. GE and GSS are described in Table 4-5, Table 4-21 and Table 4-22 respectively.

Patient 6 PCS: This 44-year-old gentleman suffered from long-standing severe symptoms of nausea, eructation, bloating, abdominal pain and early satiety. He had been under the care of upper GI consultants for the last three years. He underwent a Nissen's fundoplication in 2006 which resulted in worsening of his symptoms, and he had a reversal of this procedure in 2008. As he remained

symptomatic despite being on regular metoclopramide and PPI, he was considered an appropriate candidate for GNM. He also suffered from depression and was on venlafaxine. Pre-GNM gastric half-emptying time was 65 minutes GE and GSS are described in Table 4-6, Table 4-21 and Table 4-22 respectively.

Patient 7 WD: This 50-year-old lady suffered from gross pan-enteric dysmotility and slow gastric emptying. She suffers from intractable constipation for the last couple of years; she opens her bowel once every two weeks. She also suffered from bloating, abdominal pain and early satiety since last year. Her past medical history includes insulin dependent Diabetes, Diabetic Nephropathy, Diabetic retinopathy, Left below knee amputation, multiple CVAs. Her medications include insulin, Statins, Clopidogrel, Frusemide, Lansoprazole, Irbesartan and movical. She was investigated and confirmed not to have mechanical bowel obstruction on CT scan. Pre-operative investigations revealed the gastric half-emptying time of 235 minutes. GE and GSS are described in Table 4-7, Table 4-21 and Table 4-21 respectively.

Patient 8 RH This 22-year-old lady was referred with grossly delayed gastric emptying. She suffered from significant weight loss, severe nausea, bloating, abdominal pain and early satiety since last few years. Her past medical history includes appendectomy 2007, Asthma and weight loss four stones since January 2010. She is dependent on NG feed for last six months. Her medications include Tramadol, Buscopan, Mebeverine and Paracetamol. She was thoroughly investigated in the form of barium enema, CT abdomen, OGD and flexible sigmoidoscopy. She confirmed not to have a mechanical bowel obstruction. Pre-operative investigations revealed the gastric half-emptying time of 939 minutes. GE and GSS are described in Table 4-8, Table 4-21 and Table 4-22 respectively.

Patient 9 HL: This 41-year lady's primary symptoms were persistent nausea and intermittent vomiting for more than a year. Her past medical history includes diabetes mellitus Type 1, peripheral neuropathy, retinopathy, fibromyalgia, depression. Her medications include insulin, amitriptyline, fluoxetine, pregabalin, simvastatin, tramadol, omeprazole, metoclopramide. She was investigated and confirmed to have neuropathic gastroparesis. Pre-operative investigations revealed the gastric half-emptying time of 105 minutes. GE and GSS are described in Table 4-9, Table 4-21 and Table 4-22 respectively.

Patient 10 JA: This 68-year-old lady has been suffering from symptoms of early satiety, regurgitation and constipation for last few years and recently found to have significant weight loss. Her past medical history included oesophagectomy 14 years ago; she is on lifelong warfarin due to previous DVT and PE. She was referred due to the possibility of gastroparesis, and it was confirmed when her upper GI endoscopy showed food residue in the stomach and her gastric emptying time was delayed. She was started on the supplemental diet to get nutritional support and prevent further weight loss and planned for a trial of temporary gastric neuromodulation. Pre-operative investigations revealed the gastric half-emptying time of 294 minutes. GE and GSS are described in Table 4-10, Table 4-21 and Table 4-22 respectively.

Patient 11 BA: This 73-year-old gentleman has a longstanding history of IDDM for over eight years He has lost around 10 kg over a period of 18 months and complaining about abdominal pain, bloating, nausea and feeling week for a year. He was tolerating as much as he could orally but he was still losing weight. His other significant past surgical history included urostomy after cystectomy for bladder cancer 14 years ago; His regular medications include insulin Humalogue 50, quinine sulphate, metoclopramide, erythromycin. He underwent upper GI endoscopy that showed lots of food

residue that is endoscopic evidence of diabetic gastroparesis. There was no mechanical obstruction. Surprisingly gastric emptying time on nuclear imaging was normal despite strong clinical and endoscopic evidence of gastroparesis. GE and GSS are described in Table 4-11, Table 4-21 and Table 4-22 respectively.

Patient 12 SD: This 60-year-old lady was suffering from persistent nausea and vomiting for last three years, She had lost around 13 kilogram in three years. She denied any lower GI symptoms. Her past medical history includes COPD and hypertension; both were well controlled She underwent OGD, colonoscopy, CT colonography and MRI small bowel which were all unremarkable. The gastric emptying (GE) study showed markedly delayed GE time of 188 minutes. She had been on TPN for nutrition and planned for jejeunostomy for feeding. GE and GSS are described in Table 4-12, Table 4-21 and Table 4-22 respectively.

Patient 13 JT: This 48-year-old gentleman's main symptoms were chronic constipation for last few years and he recently developed symptoms of reflux, persistent vomiting and abdominal pain. These symptoms were progressively getting worse. His past medical history includes L5/S1 disc prolapsed. His radiological investigation confirmed slow large bowel transit, breath test confirmed slow, small bowel transit. He was referred for Gastric neuromodulation with the view that it will help his bowel symptoms as well. We attempted to get the gastric emptying study for this gentleman, but he could not tolerate it, on two occasions he vomited multiple times during the test. We decided not to attempt any further GE study test. GSS are described in Table 4-13, Table 4-21 and Table 4-22 respectively.

Patient 14 AO: This 51 years gentleman was suffering from vomiting for last eight months. These symptoms required seven admissions to the hospital in last eight months. His vomiting frequency was 20-30 times per day. It was slightly improved after starting on antiemetic's and prokinetic medications. His bowels were regular, but his appetite was reduced. His past medical history includes Type 1 diabetes mellitus for 27 years, end stage renal failure (dialysis three times per week for last one year), partial sighted left eye. His regular medications include insulin, rosuvastatin, aspirin, losartan, metoclopramide, omeprazole, erythromycin. His gastric emptying time and details of GSS are described in Table 4-14, Table 4-21 and Table 4-22 respectively.

Patient 15 DM: This 65-year-old lady suffers from abdominal discomfort after swallowing, vomiting, nausea, unable to eat and maintain her weight. She was on regular supplemental jujuneal nutrition.(1000 Kcal /day) Her past medical includes hypothyroidism and asthma. Her medications include tramadol, buscopan, pregabalin, sertraline, fentanyl patch, cyclizine and ondansetron. She was investigated, and gastric emptying study showed a rapid transit of food. Her gastric emptying time and details of GSS are described in Table 4-15, Table 4-21 and Table 4-22 respectively.

Patient 16 LL: This 53-year-old suffered from abdominal pain for last three years associated with nausea and vomiting. She recently started to lose weight. Her past medical history includes vagotomy for peptic ulcer disease 1984, hysterectomy 1991, fibromyalgia, TIA, osteoporosis and vitamin D deficiency. Her regular medication includes domperidone, omeprazole, amitryptiline, tramadol, cyclizine, cetirizine, ventolin, vitamin D3. She was allergic to penicillin and aspirin; Her gastric emptying confirmed gastroparesis with half gastric emptying time of 131 minutes. She was referred for the trial

of temporary gastric neuromodulation. GE and GSS are described in Table 4-16, Table 4-21 and Table 4-22 respectively.

Patient 17 MJB: This 45-year-old lady suffered from epigastric bloating halitosis and diarrhoea. It had started to affect her social life as she started to avoid any plans for a day out with the family. She underwent nissan fundoplication around 4-5 years ago, since then she has been having these symptoms. Other significant past medical history includes hypertension and athma. She was sensitive to many medications including erythromycin and metronidazole. Her medications include loperamide, metoclopramide, lisinopril, seretide, salbutamol, amitriptyline, ranitidine. She was investigated and confirmed to have gastroparesis with half gastric emptying time of 186 minutes. GE and GSS are described in Table 4-17, Table 4-21 and Table 4-22 respectively.

Patient 18 TF: This 38-year-old lady suffered from chronic constipation, vomiting and abdominal pain for last six years. She lost 34 kg in last six months. She had to take daily laxative. Her past medical history includes depression, abdominal hysterectomy, rectocele repair. Her investigations include upper GI endoscopy, capsule endoscopy that was normal but her colonic transit study was grossly delayed. Her regular medication includes bisacodyl, lansoprazole, and her gastric emptying study showed slightly delayed half gastric emptying time of 110 minutes. She was referred for the trial of temporary gastric neuromodulation. GE and GSS are described in Table 4-18, Table 4-21 and Table 4-22 respectively.

Patient 19 CW: This 30-years old lady known to have insulin dependent diabetes mellitus since 2007. She had problems with persistent, intractable

vomiting for one year; she had multiple admissions for ongoing vomiting. She lost six kilogram in one year. She has been extensively investigated and undergone gastroscopy, colonoscopy, and small bowel meal that were unremarkable. Her half gastric emptying time was delayed. She had tried different antiemetics including ondansetron, maxalon and domperidone, but her symptoms were not controlled.. GE and GSS are described in Table 4-19, Table 4-21 and Table 4-22 respectively.

Patient 20 SG : This 47-year gentleman had repeated admissions with abdominal pain. He had been admitted 20-30 times last year. His other past medical history includes myocarditis, spinal surgery, lumbar disc prolapse, subarachnoid haemorrhage. His regular medications include, morphine omeprazole, amitriptyline, pregabalin, erythromycin, sertraline, citalopram, metoclopramide. He has been extensively investigated, and the only abnormality was delayed gastric emptying (179 minutes). GE and GSS are described in Table 4-20, Table 4-21 and Table 4-22 respectively.

Table 4-1: Demographic data, underlying pathology and common symptoms of temporary GNM patients.

Pt. no	Gender	Age	Duration of symptoms	Aetiology and main symptoms
1	M	57	12	Annular pancreas treated with subtotal (4/5th) gastrectomy, RYGB, refashioning of RYGB.
2	M	40	3	Slow pan-enteric GI transit treated with Iliostomy. Recurrence of symptoms.
3	M	44	3	Idiopathic nausea & vomiting. Weight loss 15 kg
4	F	57	3	Long standing Diabetes mellitus (since 15 years).
5	F	54	3	Idiopathic severe nausea, bloating and abdominal pain.
6	M	44	4	Long standing Nausea, acid reflux & bloating. Treated with nissen fundoplication. Symptoms deteriorated necessitating the reversal of Nissen fundoplication.
7	F	50	2	Long standing Diabetes mellitus with Pan-enteric dysmotility
8	F	22	4	Idiopathic severe nausea, bloating, abdominal pain and significant weight loss since last few years
9	F	41	2	Persistent nausea and intermittent vomiting with long-standing Diabtes mellitus Type 1.
10	F	68	4	Post oesophagectomy 14 years ago
11	M	72	3	IDDM for over 8 years. Weight loss (around 10 kg) over a period of 18 months
12	F	60	1	Persistent nausea and vomiting for last three years. Weight loss 13 kg. TPN
13	M	49	4	Idiopathic chronic constipation for last few years and recently developed symptoms of reflux, persistent vomiting and abdominal pain.
14	M	49	1	IDDM and ESRF
15	F	66	3	Gastrectomy
16	F	53	3	Vagotomy for peptic ulcer disease 1984.
17	F	45	5	Post Nissan fundoplication around 4-5 years ago,

18	F	38	6	Idiopathic chronic constipation, vomiting and abdominal pain for last six years.
19	F	30	6	Type 1 Insulin dependent diabetes mellitus since 2007.
20	M	47	3	Idiopathic abdominal pain

4.2.2 Scintigraphy:

Scintigraphy was used for measurement of GE before and after the GNM. After an overnight fast, patients were given a test meal containing a small dose 99m Tc (0.3mSv). The meal was prepared just before the beginning of the test and consumed within 10 minutes. With patients lying supine, dynamic acquisitions were taken for 100 minutes and each image comprised anterior and posterior acquisitions. The areas of interest (AOI) were drawn on anterior and posterior images. Geometric means of radioactivity were calculated and computer-generated time activity curves were generated. Gastric half-emptying time (T50) was calculated and compared with reference values (99 ± 26 minutes) [98]

4.2.3 Follow-up

After the application of GNM, the patients were admitted to the ward for observation for 24 hours. A repeat gastric scintigraphy (GS) was performed on the first day after GNM to assess objective improvement in gastric emptying time. Patients were then sent home and requested to keep diaries of symptoms, medication and food intake for the next seven days. The patients were reviewed in the outpatient department for the removal of the wire after seven days. Repeat quality of life, weight and nutritional assessments were recorded.

4.3 Analysis / Statistics

Pre- and post-GNM data including gastroparesis symptom score (GSS), vomiting frequency score (VFS), quality of life using short form survey version 2 (SF12 V2) and gastric half-emptying time were entered into an excel

spreadsheet. Comparison between pre- and post-GNM was performed using SPSS version 17.0. The Wilcoxon test was used to determine the differences between medians.

4.3.1 Patients

Twenty patients (8 male and 12 female) were selected for the GSN. The mean age was 49 years (range 22-72). Patient characteristics and demographic data are summarized in Table 3. The average duration of their symptoms was 4 years. Thirteen of the twenty patients required multiple hospital admissions due to dehydration, electrolyte disturbances, and nutritional deficiencies. Ten patients required supplementary nutritional support by enteral and parenteral route. Eight patients had confirmed slow gastric emptying assessed by gastric scintigraphy (table 4-21).

4.4 Results

Twenty patients met the inclusion criteria and underwent temporary GNM. The procedure was performed in all twenty patients without any immediate complications. All twenty patients tolerated the wire for a week with no spontaneous dislodgement of the wire. Alterations in gastric emptying, clinical symptoms and quality of life following GNM are as follows. (Table 4-21and 4-22)

4.4.1 Gastric Emptying

Gastric half emptying time improved in 14 patients and worsened in six patients (Table 4-21) Paired t tests p value was 0.0870. It was not significant.

4.4.2 Clinical Symptoms

The gastroparesis symptoms score (GSS) improved after GNM in comparison with baseline [13 (1-19) vs. 3.5(0-8)]. Paired t tests p value was 0.0.0001. It was statistically significant. Results expressed as median (interquartile range) Vomiting frequency score (VFS) improved in 14 of the 15 symptomatic patients.

Table 4-1: Patient 1 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	17	13
a– Nausea	2	2
b– Vomiting	4	0
c– Bloating	4	4
d– Early satiety	4	4
e– Abdominal pain	3	3
Vomiting/week	30	0
Weight (kg)	58	59

Table 4-2: Patient 2 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	16	0
a– Nausea	3	0
b– Vomiting	2	0
c– Bloating	4	0

d– Early satiety	4	0
e– Abdominal pain	3	0
Vomiting/week	20	0
Weight (kg)	87.1	89.5

Table 4-3: Patient 3 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	13	4
a– Nausea	4	2
b– Vomiting	4	1
c– Bloating	1	0
d– Early satiety	3	0
e– Abdominal pain	1	1
Vomiting/week	20	3
Weight (kg)	64	65

Table 4-4: Patient 4 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	11	13
a– Nausea	2	1
b– Vomiting	2	1
c– Bloating	3	1
d– Early satiety	4	1
e– Abdominal pain	0	0

Vomiting/week	3	3
Weight (kg)	85.5	85.9

Table 4-5: Patient 5 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	13	6
a– Nausea	2	**1**
b– Vomiting	0	**0**
c– Bloating	4	**2**
d– Early satiety	3	**1**
e– Abdominal pain	4	**2**
Vomiting/week	0	**0**
Weight (kg)	69	**69.9**

Table 4-6: Patient 6 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	14	3
a– Nausea	3	0
b– Vomiting	0	0
c– Bloating	4	0
d– Early satiety	3	1
e– Abdominal pain	4	2
Vomiting/week	0	0
Weight (kg)	83.5	84

Table 4-7: Patient 7 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	13	0
a– Nausea	2	0
b– Vomiting	2	0
c– Bloating	3	0
d– Early satiety	4	0
e– Abdominal pain	2	0
Vomiting/week	3	0
Weight (kg)	67	67.4

Table 4-8: Patient 8 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	14	4
a– Nausea	3	0
b– Vomiting	1	0
c– Bloating	3	1
d– Early satiety	4	1
e– Abdominal pain	3	2
Vomiting/week	0	0
Weight (kg)	41.7	39.1

Table 4-9: Patient 9 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	11	3
a– Nausea	3	1
b– Vomiting	1	0
c– Bloating	2	1
d– Early satiety	3	1
e– Abdominal pain	2	0
Vomiting/week	3	0
Weight (kg)	56	56.6

Table 4-10: Patient 10 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	15	0
a– Nausea	2	0
b– Vomiting	2	0
c– Bloating	4	0
d– Early satiety	4	0
e– Abdominal pain	3	0
Vomiting/week	2	0
Weight (kg)	59.6	60

Table 4-11: Patient 11 GSS score

	Pre-GES	Post-GES

Total Gastroparesis Symptom Score (a–e)	10	1
a– Nausea	2	0
b– Vomiting	0	0
c– Bloating	3	0
d– Early satiety	3	1
e– Abdominal pain	2	0
Vomiting/week	0	0
Weight (kg)	56	56

Table 4-12: Patient 12 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	11	3
a– Nausea	3	0
b– Vomiting	3	0
c– Bloating	1	0
d– Early satiety	3	3
e– Abdominal pain	1	0
Vomiting/week	40	0
Weight (kg)	47	46.2

Table 4-13: Patient 13 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score	13	6

(a–e)		
a– Nausea	2	1
b– Vomiting	2	1
c– Bloating	3	2
d– Early satiety	3	2
e– Abdominal pain	3	2
Vomiting/week	35	2
Weight (kg)	80.7	80.7

Table 4-14: Patient 14 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	1	0
a– Nausea	1	0
b– Vomiting	0	0
c– Bloating	0	0
d– Early satiety	0	0
e– Abdominal pain	0	0
Vomiting/week	0	0
Weight (kg)	98.6	99.8

Table 4-15: Patient 15 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	16	8
a– Nausea	4	2
b– Vomiting	2	0
c– Bloating	3	2

d– Early satiety	4	2
e– Abdominal pain	3	2
Vomiting/week	8	2
Weight (kg)	73	74

Table 4-16: Patient 16 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	19	8
a– Nausea	4	2
b– Vomiting	4	1
c– Bloating	3	2
d– Early satiety	4	1
e– Abdominal pain	4	2
Vomiting/week	20	4
Weight (kg)	48.5	49.4

Table 4-17: Patient 17 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	9	6
a– Nausea	2	2
b– Vomiting	0	0
c– Bloating	3	1
d– Early satiety	2	2
e– Abdominal pain	2	1
Vomiting/week	0	0

Weight (kg)	80.8	81

Table 4-18: Patient 18 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	13	3
a– Nausea	2	1
b– Vomiting	1	0
c– Bloating	3	0
d– Early satiety	3	1
e– Abdominal pain	4	1
Vomiting/week	2	0
Weight (kg)	77.5	76.9

Table 4-19 Patient 19 GSS score

	Pre-GES	**Post-GES**
Total Gastroparesis Symptom Score (a–e)	13	4
a– Nausea	3	0
b– Vomiting	2	0
c– Bloating	3	2
d– Early satiety	2	1
e– Abdominal pain	3	1
Vomiting/week	5	0
Weight (kg)	49	49

Table 4-20: Patient 20 GSS score

	Pre-GES	Post-GES
Total Gastroparesis Symptom Score (a–e)	15	8
a– Nausea	3	1
b– Vomiting	4	3
c– Bloating	3	2
d– Early satiety	2	1
e– Abdominal pain	3	1
Vomiting/week	12	12
Weight (kg)	91.6	92

4.4.3 Nutritional status

All patients reported improvement in their oral intake and mean weight gain of 0.6 kg (range 0.3-2.4kg) was observed over the 7-day test period. (Table-4-21)

4.4.4 Quality of life (QOL)

Health-related quality of life QOL was assessed by SF12 questionnaire. Physical Composite Score improved in 18 patients [27.9 (22–40) vs. 37.6 (21.7–53.9)] and Mental Composite Score improved in 18 patients [31.5 (17–52.5) vs. 46.1 (17–62.1)]

Table (4-22).

Table 4-21: GSS, VFS, weight and GE before and after GNM

GSS (Gastroparesis symptom score = sum of nausea, vomiting, bloating, early satiety and abdominal pain scores)

VFS (vomiting frequency/week score).

Pt no	**GSS**		**VFS**		**Weight gain (Kg)**	**GE T1/2**	
	Pre	**Post**	**Pre**	**Post**		**Pre**	**Post**
1*	17	13	30	0	1	514	600*
2*	16	0	20	0	2.4	61	30
3*	13	3	20	3	0.3	40	50*
4*	11	4	3	3	0.9	98	41
5*	13	6	0	0	0.5	71	65
6*	14	3	0	0	0.4	65	48
7*	13	0	3	0	-2.6	235	80
8*	14	4	0	0	0.6	939	240
9*	11	3	3	0	0.4	105	85
10*	15	0	2	0	0	294	280
11*	10	1	0	0	-0.8	42	28
12*	11	3	40	0	0	188	250*
13	13	6	35	2	1.2	90	67
14	1	0	0	0	1	47	75*
15*	16	8	8	2	0.9	20	90*
16*	19	8	20	4	0.2	131	67
17	9	6	0	0	-0.6	186	18
18*	13	3	2	0	0.6	110	54
19*	13	4	5	0	0	91	69
20	15	8	12	12	0.4	179	52
Median	**13**	**3.5**	**3**	**0**	**0.6**	**105**	**67**
Mean	**12.8**	**4.1**				**175**	**88**
SD	**3.7**	**3.3**				**212**	**77**

*Subjects with significant improvement in symptom scores and **Reduced GE after GNM. Score are expressed as median unless otherwise explained.

Table 4-22: QOL before and after GNM

Pt no	PCS		MCS	
	Pre	Post	Pre	Post
1	22.8	21.7	39.1	42.6
2	38.8	52.4	52.5	62.1
3	27.2	40.5	36.7	45.2
4	27.9	28.1	24.3	29.2
5	23.4	21.1	17.1	22.8
6	32.3	53.9	33	18
7	27.5	36.2	41.6	62.1
8	25.9	30.7	17.9	45.1
9	33	45	35	54
10	22	42	41	49
11	22.4	25.2	34.8	56.7
12	29	33	17	17
13	40	45	36	47
14	32	33	48	55
15	24	27	30	37
16	25	27	23	26
17	31	42	28	47
18	38	48	17	48
19	28	50	30	59
20	32	39	19	30
Median	**27.9**	**37.6**	**31.6**	**46.1**
Mean	**29.1**	**37.0**	**31**	**42.6**
SD	**5.46**	**10.2**	**10.6**	**14.3**
p-value	**0.0001**		**0.0002**	

QOL before and after GNM; *Subjects with improved physical composite score (n = 18), mental composite score (n = 18).

4.5 Discussion:

Our experience with temporary GNM showed that GNM could be successful and safe in relieving the clinical symptoms of the patients with gastroparesis-related symptoms and it also showed objective improvement through measurements of GE.

As described in chapter two, there is conflicting data about the effectiveness of GNM. RCT conducted in 2003, did not conclusively showed significant improvement. [56]

T Abell at el [62] showed no significant change in ON and OFF period in a double masked placebo controlled trial. Macullum at el [66] showed no change in symptoms and GE. Multiple case series have been published in support of the efficacy of GNM for the gastroparesis and drug resistant nausea and vomiting [38,64,83, 85,86,94,96,106,109,104]

Recently a systematic review of the case series has been published which highlighted the outcome of the procedure in different centers across the world. [48] The review established the importance of high-frequency GNM for the treatment of resistant gastroparesis. Reduction in nausea and vomiting, nutritional support requirement and an improvement in gastric emptying were also highlighted.[53] In addition to diabetes Mellitus and idiopathic gastroparesis patients, previous studies have demonstrated beneficial results in post gastric surgery gastroparesis resistant to medical therapy treated with GNM.[64,97] There are, however only a few studies that focused on the objective changes in GE following GNM. [38,53,80, 94].The data is uncertain regarding the effect of GNM on GE.

Seven studies [58,113,114,115,116,124,125,] noted a significant improvement in GE.

On the other hand, seven studies [40,47,49,50,55,88,125] noted no significant change in GE

In one study GNM in 16 post-operative surgical patients improved GI symptoms but did not change the GE after 12 months[80]. In a different study

both liquid gastric emptying (after temporary GNM) and solid gastric emptying (after permanent GNM) improved in patients with Gastroparesis secondary to diabetes mellitus, post-surgical and idiopathic cases.[95] Other authors have also reported improvement of GE after 6 months and 1 year. [94]

Significant symptomatic improvement with no change in GE can be explained due to placebo effect of GNM. Abell et al [62] a double masked, randomized, placebo-controlled trial addressed this question but could not conclusively reject that symptomatic improvement after GNM is due to placebo effect.
Temporary GNM wire can be placed using an endoscopic approach where the electrode (wire) is brought out of the nose, whereas the other method involves the transperitoneal intramuscular (muscularis properia) approach using percutaneous endoscopic or laparoscopic technique.[111] The wire is then attached to GNM and programmed to deliver low energy high-frequency GNM as described previously. Endoscopic insertion of temporary GNM wire has become widely accepted method.

Our case series is of small numbers and consisted of patients with severe symptoms of mixed etiology. We applied temporary GNM for a short period (7 days). Each patient that included in this trail was individually selected carefully after multiple clinical assessments and extensive investigations. One of our patients had a previous history of multiple surgeries & RYGB secondary to a troublesome annular pancreas. The second patient suffered from slow transit in whole GI tract resulting in severe constipation that was initially treated with an ileostomy. After few years, the ileostomy output reduced considerably (2-3 times a week only), contents gradually became hard in consistency and fecal in nature. The third patient had suffered from long-standing diabetes. In the fourth patient, severe gastroparesis symptoms were associated with acid reflux and were therefore treated with Nissen's fundoplication. Nissen's fundoplication was then reverted as symptoms did not improve and the patient was then considered for GNM. No obvious cause could be identified for the rest of our patients though one of them lost 15 kg weight in 3 years because of inability to eat and drink properly. Normal Gastric emptying time but slow intestinal transit was recorded in this patient.

Post GNM, GE remained unchanged in this patient. In one patient we recorded exceptionally prolonged GE (table 4-21). This was also confirmed by endoscopic evaluations on multiple occasions, as the food was present in the gastric pouch several hours after the ingestion. The endoscopic assessment also revealed that the pouch tissue had become fibrotic, very friable and associated with multiple ulcers. This may be secondary to prolonged stasis of food and multiple surgeries. The possible mechanisms of extremely prolonged GE may be vagotomy, loss of normal tissue and fibrotic conversion resulting in no or abnormal gastric slow waves. GE time did not improve in this patient after GNM (table 4-21). Slow GE, an unusual finding, following GNM, was recorded in five patients, and we were unable to identify any explanation for this particular change whereas GE improved in other fifteen patients. GSS improved in eighteen patients after a GNM trial whereas vomiting frequency score did not change in two of our patients. The mixed response of GE in our patients may be because of the diverse and complex etiologies. Change in GE may have been more consistent in patients with similar etiologies and less complex surgical history. The improvement in the health related QOL was very subjective as the mental composite score improved in eighteen patients and physical composite scores also improved in eighteen patients. All patients were able to eat and tolerate more food and fluids after GNM. It was confirmed with their increased weight after test period.

The precise mechanism underlying the clinical benefits of the GNM is still not fully understood. It is suggested that the significant beneficial effects are mediated by local neurostimulation and possibly involves central nervous system. Other proposed mechanisms include gastric fundus relaxation and contribution of GI motility hormones. [113]Most of the studies, however, observed minimal improvement in gastric emptying suggesting that improved nausea and vomiting may not be due to a change in gastric emptying .[43, 45] We found that the clinical improvement was not associated with objective improvement in GE, in only five cases. However, improvement in GE time in fifteen patients within 24 hours of GNM reflects that it enhanced the GI motility.

The quick and significant response in our patients with gastroparesis, drug-resistant nausea and vomiting clearly suggest that a permanent GNM has a

potential for a long-term solution in this patient category. The cost of permanent GNM procedure is in the range of £10500. Therefore, the individual case selection for a permanent device should be a cautious process, based upon not only the subjective and objective improvements after temporary GNM, but after consideration of the overall cost and possible complications. Patient response to a temporary device can guide us in further case selection for the insertion of a permanent GNM device. Further research is required in this field to focus on the actual mechanisms of GNM and long-term consequences of the procedure.

4.6 Conclusion

Temporary GNM can improve gastroparesis related upper GI symptoms, QOL and nutritional status in patients with drug-resistant nausea and vomiting. It also improved gastric emptying in some of the patients. Thus, the precise indications for permanent GNM should be considered after a trial with temporary GNM in each patient.

5 Long-term effects of Permanent Gastric Neuromodulation.

Excerpts of this chapter were presented as a poster at the European society of surgical research 2013.

Akbar MJ, Ullah S, Avery G, Sedman P, MacFie J. Permanent gastric neuromodulation for the drug resistant gastroparesis and persistent nausea and vomiting.

5.1 Background

The symptoms of gastroparesis are non-specific and include nausea, vomiting, abdominal distension, early satiety and abdominal pain.[61, 82] These symptoms can mimic multiple illnesses .[62] Therefore, it is diagnosed after the exclusion of other organic gastric pathologies and confirmed with objective evidence of delayed gastric emptying (GE).

The treatment modalities for gastroparesis include the treatment of the underlying cause, dietary adjustment, antiemetic and prokinetic medications. Permanent gastric neuromodulation (P-GNM) has evolved as a treatment option for severe and drug-resistant gastroparesis over the last decade. The permanent gastric neuromodulation is expensive, it requires general anaesthesia and surgical procedure (laparoscopic/ laparotomy) to implant GNM device into the abdominal wall. However, there is limited data available on the effectiveness of permanent gastric neuromodulation as described in chapter 2 and chapter 4. The success rate of GNM is variable between 50-70%.[101] To improve our success rate we included patients after a successful trial of temporary GNM. In our initial study of temporary GNM twenty patients underwent temporary gastric neuromodulation out of those 11 were considered suitable for permanent GNM. We focused on multiple criteria to assess overall patient wellbeing. It included symptomatic improvement, the nutritional outcome in terms of weight gain, and health related quality of life using short form survey 12 versions 2 (SF12 V2) and objective measurement of gastric emptying during the trial period of seven days for each patient.

5.2 Method

5.2.1 Patient selection and assessment

All the patients had medical treatment for six to twelve months. After the failure of standard medical treatment in patients with resistant nausea and/or vomiting and where no correctable pathology was found, they were selected for consideration of the permanent GNM. Permanent GNM is an expensive procedure. It costs around £10500 in total. (Cost breakdown includes Enterra device with electrodes £8820, surgical cost £1200, anaesthesia cost 293 and ward cost 228).

All patients for permanent GNM has to apply for funding through exception treatment panel. Their symptoms were so debilitating that it was associated with malnutrition or impairment in quality of life. Baseline data such as gastroparesis symptom score (GSS), vomiting frequency Score (VFS), quality of life, using SF12 v2 and nutritional status were assessed in all patients. The quality of life was assessed using SF12 V2 questioner, which is a validated tool for qualitative assessment. Quality of life assessment included mental composite score (MCS) and physical composite score (PCS).

Patients with refractory nausea and/or vomiting who failed to respond to medical treatment and who responded favorably after the trial of temporary GNM were selected for consideration of permanent GNM.

Laparoscopic insertion of permanent GNM is widely accepted method although open and laparoscopic single site methods were also being used. Prophylactic antibiotic was given at the start of the procedure. In our institution, we used three-port laparoscopic approach. Two 12 mm ports were introduced at infra-umbilical region and one 6mm port was introduced in the epigastric region. Pylorus was identified, and a measuring tape was used to measure 10cm proximal to pyloric junction on the greater curvature. This point was marked, and two leads were inserted into the muscularis propria of the stomach while keeping them 1 cm apart and longitudinal to the greater curvature. At this point, upper GI endoscopy was performed to ensure that leads have not penetrated through the mucosa. Both leads were connected with GNM battery to check impedance. Once satisfied with assessment the leads were secured using non-dissolvable sutures. Both leads were brought out at left upper quadrant of abdominal wall, well away from left costal margin to

avoid any discomfort due to Permanent GNM. A cubcutaneous pocket was created for permanent gastric neuromodulation device. The pocket was irrigated with gentamycin solution. Permanent gastric neuromodulation device was connected to the leads and switched on. The device was secured to the rectus sheath using proline 2/0 suture. The redundant leads were coiled under the device to prevent accidental damage to leads at the time of the exchange of battery after 5-10 years and to avoid general anaesthesia for battery exchange procedure. Patients were kept in the hospital for the overnight stay for observation and discharged home the next day. First follow-up was performed after six weeks and then yearly follow-up afterwards.

A detailed description of the clinical background of our selected patients has been described in chapter 4.

Table 5: Demographic data, underlying pathology and common symptoms of permanent GNM patients.

Pt. no	Gender	Age	Duration of symptoms	Aetiology
1	M	57	12	Annular pancreas treated with subtotal (4/5th) gastrectomy, RYGB, refashioning of RYGB.
2	M	40	3	Slow pan-enteric GI transit treated with Iliostomy. Recurrence of symptoms.
3	M	44	3	Idiopathic nausea & vomiting. Weight loss 15 kg
4	F	54	3	Idiopathic severe nausea, bloating and abdominal pain.
5	F	41	2	Persistent nausea and intermittent vomiting with long-standing Diabtes mellitus Type 1.
6	M	72	3	IDDM for over 8 years. Weight loss (around 10 kg) over a period of 18 months
7	F	24	3	Horse riding accident. Roux-en-y pancreaticojejunostomy, post-op complications, multiple surgeries, inability to eat and drink, regular prolonged hospital admissions.
8	M	49	4	Idiopathic chronic constipation for last few years and recently developed symptoms of reflux, persistent vomiting and abdominal pain.
9	F	53	3	Vagotomy for peptic ulcer disease 1984.
10	F	38	6	Idiopathic chronic constipation, vomiting and abdominal pain for last six years.
11	F	30	6	Type 1 Insulin dependent diabetes mellitus since 2007.

5.2.2 Scintigraphy

Scintigraphy was used for measurement of GE before and after the permanent GNM. Gastric half-emptying time (T50) was calculated and compared with our reference values (99 ± 26 minutes) [98]

5.2.3 Follow-up

After the application of permanent GNM, the patients were admitted to the ward for observation and discharged home the next day. A repeat gastric scintigraphy (GE) was performed after six weeks. Patients were requested to keep diaries of symptoms, medication and food intake. The patients were reviewed in the outpatient department after six weeks and one year. Repeat health related quality of life, weight and nutritional assessments were recorded.

5.2.4 Analysis / Statistics

Pre- and post permanent GNM data including gastroparesis symptoms score, vomiting frequency score, health related quality of life assessment and gastric half-emptying time were entered into an Excel spread sheet. Comparison between pre- and post permanent GNM was performed using SPSS version 17.0. The Wilcoxon test was used to determine the differences between medians.

5.3 Results

Eleven patients (5 male and six female) met the inclusion criteria and underwent P-GNM. The mean age was 44 years (range 23-72). Patient characteristics and demographic data are summarized in Table 5. The average duration of their symptoms was four years. Four patients required multiple hospital admissions due to dehydration, electrolyte disturbances, and malnutrition. Three patients required supplementary nutritional support by enteral or parenteral routes. Three patients had confirmed slow gastric emptying assessed by gastric scintigraphy (table 5-12).

Alterations in gastric emptying, clinical symptoms and quality of life following permanent GNM were noted in all patients. (Table 5-12 and 5-13)

5.3.1 Gastric Emptying

Gastric half emptying time improved in nine patients, from baseline 105 vs 79 (table 5-12)

5.3.2 Clinical Symptoms and Nutritional Status

Results are expressed as median (interquartile range). The overall gastroparesis symptoms score (GSS) improved after GNM in comparison with baseline [13 (8-20) vs. 4(0-10)]. Vomiting frequency score (VFS) improved in all symptomatic patients. All patients reported an improvement in oral intake and a mean weight gain of 3 kg (range 0.1-7kg) was observed on first follow-up after 6 weeks. (Table-5-12)

Table 5-1: Patient 1B GSS score

	Pre-P-GNM	**Post-P-GNM**
Total Gastroparesis Symptom Score (a–e)	20	6
a– Nausea	4	2
b– Vomiting	4	0
c– Bloating	4	1
d– Early satiety	4	2
e– Abdominal pain	3	1
Vomiting/week	40	13
Weight (kg)	59	60.5

Table 5-2: Patient 2B GSS score

	Pre-P-GNM	Post-P-GNM
Total Gastroparesis Symptom Score (a–e)	17	0
a– Nausea	3	0
b– Vomiting	3	0
c– Bloating	4	0
d– Early satiety	4	0
e– Abdominal pain	3	0
Vomiting/week	4	0
Weight (kg)	90	92

Table 5-3: Patient 3B GSS score

	Pre- P-GNM	Post-P-GNM
Total Gastroparesis Symptom Score (a–e)	12	3
a– Nausea	3	0
b– Vomiting	3	1
c– Bloating	2	1
d– Early satiety	3	1
e– Abdominal pain	1	0
Vomiting/week	16	2
Weight (kg)	72	72

Table 5-4: Patient 4B GSS score

	Pre- P-GNM	**Post-P-GNM**
Total Gastroparesis Symptom Score (a–e)	12	8
a– Nausea	3	2
b– Vomiting	0	0
c– Bloating	4	2
d– Early satiety	2	2
e– Abdominal pain	3	2
Vomiting/week	0	0
Weight (kg)	60.5	67

Table 5-5: Patient 5B GSS score

	Pre- P-GNM	**Post-P-GNM**
Total Gastroparesis Symptom Score (a–e)	10	4
a– Nausea	3	**1**
b– Vomiting	1	**0**
c– Bloating	1	**1**
d– Early satiety	3	**1**
e– Abdominal pain	2	**1**
Vomiting/week	4	**0**
Weight (kg)	47.5	**51**

Table 5-6: Patient 6B GSS score

	Pre- P-GNM	Post-P-GNM
Total Gastroparesis Symptom Score (a–e)	8	3
a– Nausea	1	0
b– Vomiting	0	0
c– Bloating	2	1
d– Early satiety	3	1
e– Abdominal pain	2	1
Vomiting/week	0	0
Weight (kg)	55	53

Table 5-7: Patient 7B GSS score

	Pre- P-GNM	Post-P-GNM
Total Gastroparesis Symptom Score (a–e)	15	10
a– Nausea	2	1
b– Vomiting	4	2
c– Bloating	2	2
d– Early satiety	4	4
e– Abdominal pain	3	1
Vomiting/week	35	10
Weight (kg)	50	54.4

Table 5-8: Patient 8B GSS score

	Pre- P-GNM	Post-P-GNM
Total Gastroparesis Symptom Score (a–e)	13	4
a– Nausea	2	1
b– Vomiting	3	0
c– Bloating	3	1
d– Early satiety	2	1
e– Abdominal pain	3	1
Vomiting/week	30	0
Weight (kg)	78	82

Table 5-9: Patient 9B GSS score

	Pre- P-GNM	Post-P-GNM
Total Gastroparesis Symptom Score (a–e)	20	0
a– Nausea	4	0
b– Vomiting	4	0
c– Bloating	4	0
d– Early satiety	4	0
e– Abdominal pain	4	0
Vomiting/week	40	7
Weight (kg)	42	46

Table 5-10: Patient 10B GSS score

	Pre- P-GNM	Post-P-GNM
Total Gastroparesis Symptom Score (a–e)	18	10
a– Nausea	3	1
b– Vomiting	3	1
c– Bloating	4	2
d– Early satiety	4	2
e– Abdominal pain	4	4
Vomiting/week	10	2
Weight (kg)	70	77

Table 5-11: Patient 11B GSS score

	Pre-P-GNM	Post-P-GNM
Total Gastroparesis Symptom Score (a–e)	11	8
a– Nausea	2	2
b– Vomiting	1	2
c– Bloating	3	1
d– Early satiety	2	1
e– Abdominal pain	3	2
Vomiting/week	1	0
Weight (kg)	50	54

Table 5-12: GSS, VFS, weight and GE before and after GNM

GSS (Gastroparesis symptom score = sum of nausea, vomiting, bloating, early satiety and abdominal pain scores) VFS (vomiting frequency/week score).

Pt no	GSS		VFS		Weight gain (kg)	GE T1/2 (minutes)	
	Pre	Post	Pre	Post		Pre	Post
1*	20	6	40	13	1	514	600**
2*	17	0	4	0	2.4	61	30
3*	12	3	16	2	1	40	50**
4	12	8	0	0	0.5	71	46
5*	10	4	4	0	3.5	105	85
6*	8	3	0	0	-2	42	28
7	15	10	35	10	4.4	120	79
8*	13	4	30	0	4	106	80
9*	20	0	40	7	4	131	81
10	18	10	10	2	7	110	80
11*	11	8	1	0	4	69	37
Median	**13**	**4**	**10**	**0**	**4**	**105**	**79**

*Subjects with significant improvement in symptom scores and **GE increases in two patients after GNM. Score are expressed as median unless otherwise explained.

5.3.3 Quality of Life

Health-related quality of life was assessed by short form survey version 2 (SF12 V2) questionnaire. Physical Composite Score improved in 9 patients [31(10–44) vs. 44 (9.2–57)] and Mental Composite Score improved in 9 patients [25(18–52.5) vs. 41 (22–55)] (Table 5-14)

Table 5-13: QOL before and after GNM

Pt no	PCS		MCS	
	Pre	**Post**	**Pre**	**Post**
1	22.8	21.7	39.1	42.6
2	38.8	52.4	52.5	62.1
3	27.2	40.5	36.7	45.2
4	23.4	21.1	17.1	22.8
5	33	45	35	54
6	22.4	25.2	34.8	56.7
7	39	48	22	30
8	40	45	36	47
9	25	27	23	26
10	38	48	17	48
11	28	50	30	59
Median	**31**	**44**	**25**	**41**

QOL before and after GNM; *Subjects with improved physical composite score (n = 9), mental composite score (n = 9).

5.3.4 Follow-up

After the first review of patients, they were given one yearly follow-up appointment. Follow-up was arranged for regular assessment of their symptoms and performance after the permanent GNM. They were also encouraged to request an urgent appointment if the clinical situation changes or need arises. Only two patients requested urgent appointment due to discomfort at device implantation site and continuous symptoms. All the patients were assessed at one-year follow-up with GE study.

One-year Follow-up results are as follows.

Table 5-1F: Patient 1F GSS score

	Pre-P-GNM	**One year F/U GNM**
Total Gastroparesis Symptom Score (a–e)	20	8
a– Nausea	4	2
b– Vomiting	4	2
c– Bloating	4	1
d– Early satiety	4	1
e– Abdominal pain	3	2
Vomiting/week	40	20
Weight (kg)	59	60

Table 5-2F: Patient 2F GSS score

	Pre-P-GNM	**One year F/U GNM**
Total Gastroparesis Symptom Score (a–e)	17	2
a– Nausea	3	0
b– Vomiting	3	0
c– Bloating	4	1
d– Early satiety	4	0
e– Abdominal pain	3	1
Vomiting/week	4	0
Weight (kg)	90	97

Table 5-3F: Patient 3F GSS score

	Pre- P-GNM	One year F/U GNM
Total Gastroparesis Symptom Score (a–e)	12	4
a– Nausea	3	0
b– Vomiting	3	2
c– Bloating	2	1
d– Early satiety	3	1
e– Abdominal pain	1	0
Vomiting/week	16	4
Weight (kg)	72	81

Table 5-4F: Patient 4 FGSS score

	Pre- P-GNM	One year F/U GNM
Total Gastroparesis Symptom Score (a–e)	12	12
a– Nausea	3	3
b– Vomiting	0	0
c– Bloating	4	3
d– Early satiety	2	2
e– Abdominal pain	3	4
Vomiting/week	0	0
Weight (kg)	60.5	69

Table 5-5F: Patient 5F GSS score

	Pre- P-GNM	**One year F/U**
Total Gastroparesis Symptom Score (a–e)	10	3
a– Nausea	3	**1**
b– Vomiting	1	**0**
c– Bloating	1	**1**
d– Early satiety	3	**1**
e– Abdominal pain	2	**0**
Vomiting/week	4	**0**
Weight (kg)	47.5	**53**

Table 5-6F: Patient 6F GSS score

	Pre- P-GNM	**One year F/U**
Total Gastroparesis Symptom Score (a–e)	8	6
a– Nausea	1	1
b– Vomiting	0	0
c– Bloating	2	1
d– Early satiety	3	2
e– Abdominal pain	2	2
Vomiting/week	0	0
Weight (kg)	55	58

Table 5-7F: Patient 7F GSS score

	Pre- P-GNM	One year F/U
Total Gastroparesis Symptom Score (a–e)	15	8
a– Nausea	2	2
b– Vomiting	4	2
c– Bloating	2	2
d– Early satiety	4	0
e– Abdominal pain	3	2
Vomiting/week	35	4
Weight (kg)	50	53

Table 5-8F: Patient 8F GSS score

	Pre- P-GNM	One year F/U
Total Gastroparesis Symptom Score (a–e)	13	3
a– Nausea	2	1
b– Vomiting	3	0
c– Bloating	3	1
d– Early satiety	2	0
e– Abdominal pain	3	1
Vomiting/week	30	0
Weight (kg)	78	82

Table 5-9F: Patient 9F GSS score

	Pre- P-GNM	One year F/U
Total Gastroparesis Symptom Score (a–e)	20	16
a– Nausea	4	3
b– Vomiting	4	3
c– Bloating	4	3
d– Early satiety	4	3
e– Abdominal pain	4	4
Vomiting/week	40	30
Weight (kg)	42	44

Table 5-10F: Patient 10F GSS score

	Pre- P-GNM	One year F/U
Total Gastroparesis Symptom Score (a–e)	18	7
a– Nausea	3	1
b– Vomiting	3	1
c– Bloating	4	2
d– Early satiety	4	1
e– Abdominal pain	4	3
Vomiting/week	10	2
Weight (kg)	70	76

Table 5-11F: Patient 11F GSS score

	Pre-P-GNM	**One year F/U**
Total Gastroparesis Symptom Score (a–e)	11	0
a– Nausea	2	0
b– Vomiting	1	0
c– Bloating	3	0
d– Early satiety	2	0
e– Abdominal pain	3	0
Vomiting/week	1	0
Weight (kg)	50	60

Table 5-12: QOL after one year of Permanent GNM

Pt no	PCS		MCS	
	Pre	**1Yr F/U**	**Pre**	**1 Yr F/U**
1	22.8	14.8	39.1	59
2	38.8	47.6	52.5	60.7
3	27.2	28.6	36.7	56.6
4	23.4	22.4	17.1	31.3
5	33	41.4	35	52.2
6	22.4	20.2	34.8	59.9
7	39	38.7	22	37.7
8	40	56.7	36	41
9	25	20.4	23	26
10	38	30.2	17	34
11	28	56	30	52.4
Median	**31**	**44**	**25**	**41**

QOL before and after GNM; *Subjects with an improved physical composite score (n = 9), mental composite score (n = 9).

Table 5-13 Half gastric emptying time and weight after one year of Permanent GNM

Pt no	GE T1/2		Weight (kg)	
	Pre	**1Yr F/U**	**Pre**	**1 Yr F/U**
1	514	1000**	59	60
2	61	25	90	97
3	40	46**	72	81
4	71	28	60	69
5	105	87	47	53
6	42	30	55	58
7	120	71	50	53
8	106	79	78	82
9	131	59	42	44
10	110	61	70	76
11	69	40	50	64
Median	**105**	**59**	**59.8**	**64**

**GE increased in two patients after GNM. GE values remained stable over one year period. Score are expressed as median unless otherwise explained.

5.4 Discussion:

Our experience with permanent GNM is small, but it has shown that permanent GNM can be used in selected patients with gastroparesis-related symptoms.

Previously multiple case series have been published in support of the efficacy of GNM for the gastroparesis and drug resistant nausea and vomiting[38, 62,68,69,70,78,93] The majority of the treated patients consisted of diabetes mellitus and idiopathic gastroparesis followed by patients with post-surgical and post-

transplant gastroparesis. Within our cohort of patients, four were post-surgical, and three patients were diabetic, and the remaining 4 were idiopathic. Our experience also showed that post-surgical patients had good symptomatic improvement and our patients who were previously requiring parenteral or elemental nutrition after permanent GNM maintained themselves without any nutritional support. Their number of hospital admissions also reduced to zero. There are, however, only a few studies that focused on the objective changes in GE following permanent GNM.[40,47,49, 78] The data is uncertain concerning the effect of GNM on GE. In one study GNM in 16 post-operative surgical patients improved GI symptoms but did not change the GE after 12 months.[64] This observation was also noted in our first patient who undergone multiple surgeries be-fore and his GI symptoms improved markedly but GE did not change. In a different study both liquid gastric emptying (after temporary GNM) and solid gastric emptying (after permanent GNM) improved in patients with Gastroparesis secondary to diabetes mellitus, post-surgical and idiopathic cases. [95] Other authors also have reported improvement of GE after six months and one year. [78]

Laparoscopic insertion of permanent GNM is widely accepted method although open and laparoscopic single site method is also being used.

A recent study has shown that is a safe and efficient way for permanent GNM. Post op complications mainly around the subcutaneous pocket site are 9%, in our study two patients had some anterior abdominal wall discomfort at the implantation site of permanent GNM, but it settled with conservative management. We did not have to explant any device, and there was no case of surgical site infection.

In most cases temporary GNM showed significant benefits and then it was replaced by a permanent device. But in some cases, permanent devices were placed without any initial trial of temporary GNM.[53] Placement of a permanent electrode is an invasive procedure, and it requires open or laparoscopic abdominal surgery.[78,96] The permanent GNM has additional complication risks such as infection, device erosion, pain at the implantation site, perforation of the stomach/intestine, device migration and volvulus secondary to wires.[41,53,70] An overall complication rate of 8.3% has been reported in the literature.[42] Device explanation rate due to continued symptoms was 12%. In our study

two patients had some anterior abdominal wall discomfort at the implantation site of permanent GNM but it settled with conservative management. We did not have to explant any device, and there was no case of surgical site infection.

Our case series is of small numbers and consisted of patients with severe symptoms of mixed etiology. Each patient who included in this study was individually selected after multiple clinical assessments and extensive investigations. Gastroparesis symptoms score improved in all patients, whereas vomiting frequency score also changed in all but one patient. The mixed response of GE in our patients may be because of the diverse and complex etiologies. Change in GE may have been more consistent in patients with similar etiologies and less complex surgical history. The improvement in the health related quality of life was very subjective as the mental composite score improved in all eleven patients and physical composite scores improved in eight patients. All patients were able to eat and tolerate more food and fluids after permanent GNM. This was confirmed by the increased median weight of 5kg at one-year follow-up.

The actual mechanism underlying the clinical benefits of the permanent GNM is still not fully understood. It is suggested that the significant beneficial effects are mediated by local neurostimulation and possibly involves central nervous system. Other proposed mechanisms include gastric fundus relaxation and contribution of GI motility hormones.[97]Most of the studies, however, observed minimal improvement in gastric emptying suggesting that improved nausea and vomiting may not be due to a change in gastric emptying.[27.96]We noted that in only one case the clinical improvement was not associated with objective improvement in GE. However, improvement in GE time in nine patients at six weeks and one-year follow-up reflects that it enhanced the GI motility.

The significant response in our patients with gastroparesis related symptoms, drug-resistant nausea and vomiting clearly suggest that a permanent GNM has a potential for a long-term solution in these patient. The cost of permanent GNM procedure is in the range of £10500. Therefore, the individual case selection for a permanent device should be based upon not only the subjective and objective improvements after temporary GNM, but after consideration of

the overall cost and possible complications. Patient response to a temporary device can guide us in further case selection for the insertion of a permanent GNM device. Further research is required in this field to focus on the actual mechanisms of GNM and long-term consequences of the procedure.

5.5 Conclusion:

Permanent GNM showed long-term improvement in gastroparesis-related symptoms, quality of life and nutritional status. It also improves gastric emptying in some of these patients.

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