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Horizon scanning technology prioritising summary

Intra-abdominal vagal blocking (VBLOC™ Therapy) for obesity

August 2009



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**Australian
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of New
Interventional
Procedures -
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PRIORITISING SUMMARY

REGISTER ID S000098

NAME OF TECHNOLOGY INTRA-ABDOMINAL VAGAL BLOCKING (VBLOC™ THERAPY)

PURPOSE AND TARGET GROUP WEIGHT CONTROL IN OBESE PATIENTS

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- | | |
|--|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input checked="" type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes
- No
- Not applicable

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
USA	✓		
Australia	✓		
Mexico	✓		
Norway	✓		
Switzerland	✓		

IMPACT SUMMARY

Intra-abdominal vagal blocking (VBLOC™ therapy) uses the Maestro™ System (EnteroMedics Inc., St Paul, MN, USA) to emit high-frequency, low energy electrical signals that intermittently block vagus nerve transmission and induce weight loss in obese patients. VBLOC therapy offers a reversible and minimally invasive alternative to surgical treatments.

BACKGROUND

Overweight and obesity are defined as abnormal or excessive fat accumulation that may cause adverse health effects. Overweight and obesity are generally defined as a body mass index (BMI) of at least 25 kg/m² or 30 kg/m², respectively, BMI is a simple index of weight-for-height that is commonly used in classifying overweight and obesity in adult populations or individuals. BMI is a measure of the weight in kilograms divided by the square of the height in metres (WHO 2006). Obesity is a multifactorial disease that may have a variety of underlying causes, including physical illness, genetics, behavioural and psychological factors, and lifestyle choices. Obesity is associated with an increased risk for a number of comorbidities including diabetes, cardiovascular disease, high blood pressure, stroke, high cholesterol, obstructive sleep apnoea, osteoarthritis, and some cancers (Buchwald et al 2004; ABS 2008).

Conventional methods of weight loss have typically included diet modification, exercise, and/or pharmacotherapy. Over the last 30 years, bariatric surgery has become increasingly popular to achieve weight loss in obese patients (Buchwald et al 2004). Common bariatric procedures include, among others, isolated sleeve gastrectomy, adjustable gastric banding and gastric bypass. These treatments are more effective in achieving weight loss than conventional modalities (Colquitt et al 2009). Bariatric procedures can be carried out through open (traditional) surgery or the less invasive method of laparoscopic (keyhole) surgery. However, serious adverse events may occur, such as pulmonary embolism, and some post-operative deaths have been reported (Colquitt et al 2009). In order to reverse the effects of bariatric surgery, more invasive surgery is required.

The vagus nerve runs from the brain through the face to the thorax and abdomen. Its possible role in appetite regulation was suggested by research in which the inadvertent damage of the vagus nerve after antireflux surgery resulted in suppressed appetite, bloating, abdominal pain, flatulence, and diarrhoea (Balaji et al 2002). Recent studies have demonstrated a positive association between the levels of plasma pancreatic polypeptide (PP) after sham feeding and vagal integrity (Balaji et al 2002). A number of animal and human studies have also suggested that surgically cutting the vagus nerve (vagotomy) alters preferences for certain foods, and decreases fluid intake (Kral et al 1978; Camilleri et al 2008). Camilleri et al (2008) reported that the application of high-frequency electrical currents causes reversible inhibition of vagus and sciatic nerve propagation in rats, as well as reversible inhibition of pancreatic exocrine secretion and gastric contractions in pigs.

These observations led to the development of VBLOC therapy, which aims to achieve weight loss by utilising a less invasive form of vagal inhibition than vagotomy. VBLOC therapy is administered with the Maestro SystemTM, which consists of two implantable flexible leads with electrodes. The electrodes are placed laparoscopically, under general anaesthesia, at the anterior and posterior intra-abdominal vagal nerve trunks and connected to an implantable neuroregulator that is placed subcutaneously on the abdominal wall below the rib margin. The neuroregulator is powered by an internal

rechargeable battery. A mobile, external controller that is connected via a small, flexible cable to a cutaneous transmit coil positioned over the implanted device allows the clinician to control and upload information from the device (Clinical Trials 2009b). Treatment can be reversed by simply turning off the neuroregulator. The proponents of VBLOC therapy suggest that it may offer more effective long-term weight reduction than current pharmacotherapy or behavioural modification techniques.

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of overweight and obesity in the Australian population has been increasing for the last 20 to 30 years (AIHW 2008). In the most recent National Health Survey (2004 – 2005), over half of Australians were either overweight (BMI ≥ 25 but <30) or obese (BMI ≥ 30). From this survey, an estimated 2.5 million Australians who were 18 years of age or older were classified as obese (19% males; 17% females), and 4.9 million were classified as overweight (41% males; 25% females). High BMI was associated with 7.5% of the burden of disease and injury in the Australian population in 2004-2005 (ABS 2008).

DIFFUSION

While VBLOC therapy is still at an early stage of development, two human trials of VBLOC therapy for the treatment of obesity are currently being conducted (ClinicalTrials 2009a; ClinicalTrials 2009b).

The Maestro System is not presently approved by the US Food and Drug Administration or listed with the Australian Therapeutic Goods Administration. EnteroMedics obtained CE marked approval in Europe in 2009 which entitles the company to market the Maestro System to countries of the European Economic area. An international prospective cohort study assessing the safety and efficacy of this device is currently underway (Clinical Trials 2009b). A second multi-centre randomised controlled trial comparing intervention to control (implantable device received with VBLOC therapy turned OFF) commenced in August 2007, with an expected completion date of June 2013 (Clinical Trials 2009a).

Several additional studies investigating parameters such as medical weight management programs, gastric functioning and clinical performance of the Maestro System are underway or complete. The authors have published abstracts in peer-reviewed journals or in various conference proceedings; however, full peer-reviewed journal articles on these studies are not currently available (EnteroMedics Inc., 2009).

COMPARATORS

Management of obesity is concerned with providing the optimum loss of excess weight. There are currently many types of interventions. Bariatric surgery is an option for obese patients when other conservative or non-invasive methods of weight loss (e.g., behavioural or pharmacotherapy interventions) have been unsuccessful. This type of surgery is performed under general anaesthesia.

Comparative surgical procedures for VBLOC include:

- Sleeve Gastrectomy: This procedure is generally a two part procedure: firstly, the vertical division of the stomach (reduction to approximately 25% of its size) leaving the pyloric valve unaltered thus preserving stomach function and digestion; and secondly, may involve gastric bypass or duodenal switch. Reported complications include leaking or vomiting due to overeating (Colquitt et al 2009).
- Gastric Bypass (Roux-en-Y): These techniques combine restrictive and malabsorption techniques by using surgical stapling to create a partition of the stomach with a small outlet to the intestine and often a prosthetic bypass is included to stabilise the gastroenterostomy. Complications can include, among others, failure of surgical stapling, leaking of the gastric or intestinal junction, acute gastric dilatation, or delayed gastric emptying (Colquitt et al 2009).
- Gastroplasty: Vertical band gastroplasty is a restrictive procedure that uses surgical stapling to create a small partition along the top of the stomach to create a small stoma, and complications (e.g., bolus obstruction, anemia, leakage, stenosis, ulcers, etc) are reported to be relatively rare (Colquitt et al 2009).
- Gastric Banding: This procedure includes placing a constricting ring around the top end (fundus) of the stomach, and complications may include, among others, those associated with the operative procedure, splenic injury, oesophageal injury, band erosion or migration.
- Biliopancreatic Diversion: This is primarily a malabsorptive technique which includes the removal of part of the stomach to limit oral intake and induce weight loss, and this procedure is associated with higher rates of morbidity and mortality (2%) compared with the other procedures (Colquitt et al 2009).

SAFETY AND EFFECTIVENESS ISSUES

Study description

Two clinical studies were identified (Camilleri et al 2008; Camilleri et al 2009) for inclusion in this prioritising summary. Camilleri et al (2008) was a prospective, multicentre case series study of 31 obese patients (mean BMI 41.2 kg/m², standard deviation (SD) 1.4) who received VBLOC therapy at the oesophagogastric junction (ECJ). Patients were included if they were unable to achieve satisfactory weight loss with conventional medical management, which included dietary counselling, behaviour/exercise modification, and pharmacotherapy. Women of reproductive age were also included if a negative pregnancy test was confirmed and a contraception regimen was followed throughout the study. Exclusion criteria included the presence of type 1 or type 2 diabetes mellitus in poor control or with autonomic neuropathy, including gastroparesis; smoking cessation or weight loss drug therapy within the previous 3 months; a reduction of >10% of the patient's body weight in the previous 12 months; and, previous or concurrent conditions that would preclude device placement, such as prior gastric resection or major abdominal surgery (except for cholecystectomy or hysterectomy), clinically significant hiatal hernia or intraoperatively determined hiatal hernia requiring surgical repair or extensive dissection at the ECJ at time of surgery, or presence of another electrical-powered medical device or implanted gastrointestinal device or prosthesis. No losses to follow-up were reported.

Camillera et al (2008) reported laparoscopic implantation of the device took approximately 60 to 90 minutes. The external controller was programmed at a therapeutic frequency of 5000 Hz and an amplitude ranging from 1 to 6 mA. The device was programmed using an algorithm of 5 minutes “blocking” alternating with 5 minutes “without blocking” for 12 hours per day. The primary outcome measure was percentage of excess weight loss (EWL) calculated by dividing weight lost by the excess body weight and multiplying by 100. Excess body weight was calculated by subtracting the patient’s ideal body weight (relative to a BMI of 25) from their total body weight. Patients were assessed at 4 weeks, 12 weeks, and 6 months (Camilleri et al 2008).

Two substudies were performed. The first substudy (n=10 patients) in one centre quantified changes in caloric intake, dietary composition, satiation at meals, and satiety (reduced hunger) between meals. Measurements were taken at baseline, 4 weeks, 12 weeks, and 6 months of vagal blocking. Visual analog scales (VAS) were used to assess satiation and satiety using 24-hour and 1-week recall. The second substudy (n=24) was conducted in two centres after 12 weeks of vagal blocking to assess the level of vagal inhibition.

Initially, the study by Camilleri et al (2009) retrospectively analysed data from Camilleri et al (2008) and found a statistically significant association between the therapy algorithms of 90 to 150 seconds’ duration and greater percentage EWL compared with therapy algorithms of shorter or longer duration (P<0.01). On the basis of this analysis, a 120 second “on” time was chosen alternating with a 5-minute rest period for 12 hours per day, with the device being activated 2 weeks after implantation.

In the second phase of this study, 27 patients (BMI 39.3kg/m², (SD) 0.8) ; mean age 40.4 years, (SD) 1.8) were recruited prospectively at 3 centres. Inclusion and exclusion criteria were the same as Camilleri et al (2008). The implantation protocol was also similar, except that a second-generation device was used. The patients were followed up weekly for 4 weeks, fortnightly up to 12 weeks, and monthly thereafter to 6 months. The physical examinations completed at each follow-up visit included an assessment of body weight and any adverse events. Haematologic and clinical chemistry parameters, including lipase and amylase levels, and 12-lead electrocardiogram results were also monitored. Questionnaires were completed by each patient to evaluate satiation and satiety at the 4-week, 12-week and 6- month visits. The primary end-point for the study was the mean percentage of EWL at each follow-up period.

Safety

Camilleri et al (2008) reported that there were no deaths or serious adverse events related to VBLOC therapy and that no unanticipated adverse device effects occurred during the study. Three patients had serious adverse events unrelated to the device or VBLOC therapy that required brief hospitalisation: post-operative lower respiratory tract infection (n=1, length of hospital stay = 3 days); subcutaneous implant site seroma (n=1; length of hospital stay = 3); *Clostridium difficile* diarrhoea (n=1; 2 weeks into trial period; length of hospital stay = 5 days). These adverse events resolved and all three

patients continued in the study. None of the patients experienced any clinically significant changes in clinical chemistry or electrocardiogram results during the 6-month trial. Small decreases in heart rate and systolic and diastolic blood pressure were observed, but these were not considered clinically significant. None of the patients experienced organ perforation, significant bleeding, postoperative intraperitoneal infections, electrode migration, or tissue erosion.

Similarly, Camilleri et al (2009) reported no deaths, unanticipated adverse device effects, or medically serious adverse events during the trial. One patient (3.7%) was hospitalised overnight for a localised seroma with pain at the site of the subcutaneous device implantation pocket.

Efficacy

Camilleri et al (2008) reported mean percentage of EWL of 7.5% at 4 weeks, 11.6% at 12 weeks, and 14.2% at 6 months after device implantation ($P < 0.001$ compared with baseline weight for all time points). Ten percent of patients had $>30\%$ EWL and 25% had $>25\%$ EWL at 6 months; several patients had no weight loss. In a substudy of 10 patients, calorie intake decreased by $>30\%$ at 4 weeks, 12 weeks, and 6 months ($P < 0.01$ compared to baseline for all time points), while the relative amounts of carbohydrate, protein, and fat intake remained stable. Patients reported earlier satiation (fullness) at main meals ($P < 0.001$) and enhanced satiety (decreased hunger) between meals ($P = 0.005$) as indicated by results of a VAS questionnaire.

Measures of vagal function in a subset of 24 patients showed that before implantation, sham feeding resulted in a normal PP response (increase of ≥ 25 pg/mL over baseline or 42 ± 19 pg/mL) (Camilleri et al 2008). However, the plasma PP response at 20 minutes was suppressed in these patients after 12 weeks of vagal blocking, with the increase in plasma PP achieving an average of < 25 pg/mL (20 ± 7 pg/mL). Blunted PP response (< 25 pg/mL) was reported in 88%, 79%, 71%, and 67% of patients at 5, 10, 15, and 20 mins, respectively. Fourteen patients who did not experience a plasma PP > 25 pg/mL during fasting had significantly greater weight loss compared with the 10 patients who did have a plasma PP rise > 25 pg/mL on fasting ($P = 0.02$).

Camilleri et al (2009) reported that 24 of the 27 patients (88.9%) reached the 6-month study visit. Of the three patients who dropped out, 1 patient discontinued after a motor vehicle accident, but had not used the device, and 2 discontinued the trial for personal reasons. The latter 2 patients were dissatisfied with the treatment outcome despite achieving 5.9% and 11.4% EWL at 3 and 5 months, respectively, at the time of withdrawal from the study. None of these patients reported any adverse events. The % EWL at 4 weeks, 12 weeks and 6 months after device implantation was 11.0% (SD 1.3%), 18.4% (SD 2.1) and 22.7% (SD 3.1), respectively ($P < 0.001$ compared with baseline; $n = 24$). The mean decrease in BMI at 4 weeks, 12 weeks and 6 months was 1.5 kg/m^2 (SD 0.2), 2.5 kg/m^2 (SD 0.3) and 3.2 kg/m^2 (SD 0.4), respectively ($P < 0.001$ for all time points compared with baseline). At 6 months, a greater mean percentage of EWL was achieved (22.7%, SD 3.1, $n = 24$) compared with the initial study by Camilleri

et al (2008) (14.2%, SD 2.2, n=31) equating to a 59.9% greater mean percentage EWL with the second generation device ($P<0.03$). Waist circumference was significantly lower at 6 months compared with baseline values (mean reduction 8.4 cm, SD 1.5 cm; $P<0.001$, n=20). The mean reduction of 8.5 mmHg (SD 4.7) in systolic blood pressure and 2.8 mmHg (SD 2.5) in diastolic blood pressure was of clinical interest, but was not statistically significant ($P=0.09$ and $P=0.28$, respectively). Results from the questionnaires demonstrated earlier satiation at main meals ($P<0.01$) and enhanced satiety between meals ($P=0.002$) at the 6-month study visit. The changes in satiety and satiation found to be statistically significant at the 4-week visit remained significant at the 6-month period.

Metabolic measures of liver function demonstrated that both alkaline phosphatase and alanine aminotransferase were significantly lower at 6 months compared with baseline ($-6.3\pm 2.2\text{U/L}$ and $-10.1\pm 3.8\text{U/L}$, n= 19 and n=20, $P=0.009$ and $P=0.02$, respectively) (Camilleri et al 2009). Aspartate aminotransferase was also slightly lower at 6 months ($P=0.18$). Camilleri et al (2009) suggested the latter results were an indication of improvements in the liver function indexes. Although it was reported that no clinically significant changes occurred in clinical chemistry, hematologic, or electrocardiogram findings, these data were not presented.

COST IMPACT

There was no cost-effectiveness information available on VBLOC therapy due to the experimental nature of this treatment. However, VBLOC therapy is expected to cost about \$20,000 in Australia (The Australian, 2007).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

It should be noted that in the first study by Camerilli et al (2008), one of the fifteen authors received consulting fees as part of a business alliance between the Mayo Clinic and EnteroMedics Inc. Four other authors are consultants of EnteroMedics Inc, and a further three are employees of EnteroMedics Inc. In the second study by Camerilli et al (2009), one of the nine authors is an employee of EnteroMedics Inc. and five are paid consultants for EnteroMedics. Both studies were funded by EnteroMedics Inc.

SUMMARY OF FINDINGS

Preliminary evidence suggested that VBLOC therapy may be an effective and safe method of inducing weight loss in obese patients. Two case series studies found that VBLOC therapy achieved statistically significant weight loss, a reduction in caloric intake, earlier satiation, and reduced hunger relative to baseline in obese patients. Lower plasma PP levels were associated with greater weight loss, indicating that vagal inhibition had occurred. No significant adverse events were observed in relation to VBLOC therapy. However, the results of these studies should be interpreted

conservatively given that they were not comparative and the sample sizes were small. Long-term comparative studies are required to evaluate the durability of the treatment effect compared with conventional treatment strategies and to determine which patients would most benefit from VBLOC therapy.

HEALTHPACT ACTION

Based on the limited evidence available, the effectiveness of VBLOC remains unproven. Further assessment of this technology will not be conducted.

NUMBER OF STUDIES INCLUDED

Total number of studies	2
Level IV intervention evidence	2

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SEARCH CRITERIA TO BE USED

VBLOC therapy

Intra-abdominal vagal blocking

EndoMedics Maestro System