Vagal Nerve Blocking to Treat Obesity and the Metabolic Syndrome

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Weight loss clinical trials: Outcomes
Review of 80 studies with minimum 1 year follow-up (69% completion)

Look AHEAD trial: does weight loss reduce mortality?

- Randomized controlled trial: uses strategy of weight loss in patients with type 2 diabetes to achieve treatment goals
- Intensive Lifestyle Intervention (ILI) versus Diabetes Support and Education (DSE): 5,145 participants in 16 centers
- The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization
- Weight loss 6% in the intensive group vs 3.5% in the medical group with modest improvements in HbA$_{1c}$
- No difference in primary outcome at mean follow-up 9.6 years: trial was stopped

Do we need more weight loss?

# DSS: Baseline data

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>IMM (n=60)</th>
<th>RYGB (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>49 (8)</td>
<td>49 (9)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>34 (57)</td>
<td>38 (63)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>34.3 (3.1)</td>
<td>34.9 (3.0)</td>
</tr>
<tr>
<td>Waist circumference (cm), mean (SD)</td>
<td>113 (12)</td>
<td>114 (10)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean (SD)</td>
<td>132 (14)</td>
<td>127 (15)</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA\textsubscript{1c} (%)</td>
<td>9.6 (1.2)</td>
<td>9.6 (1.0)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>105 (43)</td>
<td>103 (36)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>42 (9)</td>
<td>41 (1)</td>
</tr>
<tr>
<td>Taking insulin, n (%)</td>
<td>26 (43)</td>
<td>37 (62)</td>
</tr>
<tr>
<td>Medications to achieve targets, mean (SD)</td>
<td>4.4 (1.5)</td>
<td>4.1 (1.9)</td>
</tr>
</tbody>
</table>

BMI, body mass index; DSS, Diabetes Surgery Study; HDL, high density lipoprotein; IMM, intensive medical management; LDL, low density lipoprotein; RYGB, Roux-en-y gastric bypass

Modern surgical options

- Adjustable band
- Sleeve gastrectomy
- Roux-en-Y gastric bypass (RYGB)
- Duodenal switch
## DSS: Improvement in metabolic parameters

<table>
<thead>
<tr>
<th>Glycemia</th>
<th>IMM</th>
<th>RYGB</th>
<th>Difference with p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>7.8 (7.4–8.2)</td>
<td>6.3 (6.1–6.5)</td>
<td>1.5 (1.0 – 1.9); p&lt;0.001</td>
</tr>
<tr>
<td><strong>HbA1c &lt;6.0%</strong></td>
<td>5 (9) [3–20]</td>
<td>25 (44) [31–58]</td>
<td>-35 [-50 – -20]; p&lt;0.001</td>
</tr>
<tr>
<td><strong>Fasting glucose (mg/mL)</strong></td>
<td>153 (137–169)</td>
<td>111 103–120</td>
<td>42 (23 – 60); p&lt;0.001</td>
</tr>
<tr>
<td><strong>LDL (mg/dL)</strong></td>
<td>89 (80–97)</td>
<td>83 (77–90)</td>
<td>5 (-5 – 16); p=0.27</td>
</tr>
<tr>
<td><strong>HDL (mg/dL)</strong></td>
<td>42 (39–44)</td>
<td>50 (47–54)</td>
<td>-9 (-13 – -4); p&lt;0.001</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dL)</strong></td>
<td>182 (142–222)</td>
<td>104 (92–117)</td>
<td>78 (36 – 120); p&lt;0.001</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>124 (121–127)</td>
<td>115 (112–119)</td>
<td>8 (4 – 13); p&lt;0.001</td>
</tr>
</tbody>
</table>

DSS, Diabetes Surgery Study; HDL, high density lipoprotein; IMM, intensive medical management; LDL, low density lipoprotein; RYGB, Roux-en-y gastric bypass

Complications of RYGB: Timeline

- GI bleeds
- Weight gain
- Nutritional complications
- Cholelithiasis
- Wernicke's type polyneuropathy
- Incisional hernia
- Marginal ulcers
- Anastomotic strictures
- Intestinal obstruction: internal hernias; adhesion obstruction
- Acute gastric dilatation
- Intestinal leaks
- Pulmonary embolism
- Rhabdomyolysis
- Atelectasis
- Apneic arrest
- GI bleed

Complications causing severe morbidity or >50% mortality

Less morbid complications

Note: Time is not represented to scale
Treatment Gap

Diet, Exercise, & Lifestyle Modification

- Difficult to achieve significant weight loss
- Difficult to maintain weight loss

Drug Therapy

- Lack of compliance
- Difficult to maintain weight loss
- Risks:
  - Serotonin syndrome
  - Pulmonary hypertension
  - Cognitive effects
  - Birth defects
  - Drug-drug interactions

Bariatric Surgery

- Significant dietary restrictions
- Risks:
  - Vomiting
  - Leaks
  - Bleeding
  - Bowel obstruction
  - Band erosion
  - Malabsorption
  - Constipation
  - Dumping syndrome

LARGE TREATMENT GAP

MOST PATIENTS RECEIVE SUB OPTIMAL TREATMENT
Type 2 Diabetes

- ↓ Insulin secretion
- ↑ Glucagon
- ↓ GLP-1 secretion
- ↓ Insulin action
- ↓ Glucose effectiveness

Potential mechanisms whereby bariatric surgery ameliorates diabetes

- Caloric Restriction
- Malabsorption
- Altered Incretin Hormone Secretion (↑ GLP-1 secretion)
- Altered Vagal Function

Courtesy of Adrian Vella, Mayo Clinic
Effects of surgical vagotomy

- On satiation and weight loss are often transient
- In experimental animals, accommodation reflex recovered 4 weeks post-vagotomy, through unclear metabolic or neural pathways

Science Underlying Vagal Block

10-20% of vagus nerve fibers send instructions from the brain to the gut

- Gastric acid secretion
- Digestive enzyme secretion
- Gastric capacity/motility
- Glucose regulation

SENSORY
- Satiety (Hunger)
- Satiation (Fullness)
- Energy metabolism
- Blood pressure regulation

80-90% of vagus nerve fibers send instructions from the gut to the brain

- Gastric acid secretion
- Digestive enzyme secretion
- Gastric capacity/motility
- Glucose regulation
Maestro® RF and Rechargeable Systems

- Delivers intermittent 5kHz pulses 2 min ON/1min OFF/2 min ON and 5 min OFF 12 hrs/day
- Laparoscopic vagal lead placement
- Subcutaneous neuroregulator

RF Neuroregulator

RC Neuroregulator

Lead head

Leads
Fullness and Decreased Food Intake
- Limits gastric expansion thus reducing meal size
- Delays gastric emptying for longer fullness (reduced appetite)

Energy Metabolism
- Inhibits enzymes to reduce digestive efficiency
- Helps normalize glucose production, controlling diabetes

Hunger and Satisfaction
- Suppresses appetite
- Addresses mind-body link

Vbloc® therapy: target the causes of overeating
EMPOWER (2008-2013)

- Prospective, double blind, placebo controlled randomized trial in 294 Subjects
- BMI range 35 to 39.9 with co-morbidity; 40 to 45 with or without
- Used 1st generation device with external power source
- 3% device or implant SAE rate, no therapy SAEs
- Clinically significant weight loss was observed in patients who used the device ≥ 9 hours per day in both arms
- An unanticipated therapeutic effect appeared to have been delivered to subjects in the control arm

ReCharge (2011-2016)

- Prospective, double blind, placebo controlled, randomized trial in 233 subjects, same BMI range as EMPOWER
- Built on previous trial learning
  - Uses 2nd generation device with internal power source, 12+ hrs therapy delivery
  - No charge delivered to vagus nerve in surgical sham control arm
- Showed superior weight loss in VBLOC group compared to control (p=.002) and significant level of responders
- Met safety endpoint (safer than AGB)
- Published in JAMA Fall 2014
- CE marked, TGA approval and FDA approved (as of Jan 14, 2015)
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>VBLOC</th>
<th>Sham Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td>47.1 ± 10.3</td>
<td>46.6 ± 9.4</td>
</tr>
<tr>
<td>Female</td>
<td>87.0%</td>
<td>80.5%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>92.0%</td>
<td>94.8%</td>
</tr>
<tr>
<td>African American</td>
<td>4.9%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Other</td>
<td>3.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Type 2 Diabetic</td>
<td>5.6%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Obese before Adulthood</td>
<td>44%</td>
<td>52%</td>
</tr>
</tbody>
</table>

### Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>VBLOC Mean ± SD (Range)</th>
<th>Sham Control Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>41 ± 3 (34-46)</td>
<td>41 ± 3 (35-48)</td>
</tr>
<tr>
<td><strong>Weight (lbs)</strong></td>
<td>247 ± 29 (175-349)</td>
<td>254 ± 31 (196-352)</td>
</tr>
<tr>
<td><strong>Excess weight, BMI method (lbs)</strong></td>
<td>96 ± 19 (51-161)</td>
<td>99 ± 21 (59-145)</td>
</tr>
<tr>
<td><strong>Waist circumference (in)</strong></td>
<td>48 ± 5 (36-60)</td>
<td>48 ± 4 (39-58)</td>
</tr>
</tbody>
</table>
Sustained Weight Loss with Vagal Nerve Blockade but Not with Sham: 18-Month Results of the ReCharge Trial

In Press, 2015.
VBLOC Patients Achieved Higher %EWL at 12 Months

Odds Ratio [95% CI]

<table>
<thead>
<tr>
<th>%EWL Threshold</th>
<th>VBLOC</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>2.3 [1.3, 4.1]</td>
<td>2.0 [1.1, 3.8]</td>
</tr>
<tr>
<td>25%</td>
<td>2.0 [1.0, 3.8]</td>
<td>2.0 [1.0, 3.8]</td>
</tr>
<tr>
<td>30%</td>
<td>5.0 [1.7, 14.7]</td>
<td>13.2 [1.8, 99.6]</td>
</tr>
</tbody>
</table>

% Patients [95% CI]

- 20%: VBLOC 50% [48%, 52%], Sham 30% [28%, 32%]
- 25%: VBLOC 40% [37%, 43%], Sham 28% [25%, 31%]
- 30%: VBLOC 30% [28%, 33%], Sham 20% [18%, 23%]
- 40%: VBLOC 20% [18%, 23%], Sham 15% [12%, 18%]
- 50%: VBLOC 10% [8%, 13%], Sham 8% [5%, 11%]

≈ %TBL Threshold

- 7.5%
- 9.4%
- 11.3%
- 15.1%
- 18.9%

ITT Population, LOCF
## Clinically Relevant Changes in Risk Factors for VBLOC Patients Achieved

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>VBLOC Mean Change</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>7.5% TBL</td>
<td>10% TBL</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>-5</td>
<td>-8</td>
<td>-9</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>-3</td>
<td>-5</td>
<td>-6</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>-4</td>
<td>-4</td>
<td>-6</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>-9</td>
<td>-12</td>
<td>-15</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>-5</td>
<td>-8</td>
<td>-9</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-21</td>
<td>-32</td>
<td>-41</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Waist circumference (inches)</td>
<td>-4</td>
<td>-6</td>
<td>-7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.3</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

*Post Hoc Analysis, As-Observed*
Change in Elevated DBP and SBP

**Baseline = 86±3mmHg**

<table>
<thead>
<tr>
<th></th>
<th>1 Wk</th>
<th>4 Wk</th>
<th>12 Wk</th>
<th>6 Mo</th>
<th>12 Mo</th>
<th>18 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP change</td>
<td>-35</td>
<td>-30</td>
<td>-25</td>
<td>-20</td>
<td>-15</td>
<td>0</td>
</tr>
<tr>
<td>SBP change</td>
<td>-5</td>
<td>0</td>
<td>-10</td>
<td>-15</td>
<td>-20</td>
<td>-25</td>
</tr>
</tbody>
</table>

* p=0.02

Baseline = 138±4mmHg

n=6

Toouli et al. OSSANZ conference, April 11-13, Darwin, Australia, 2012
Reversibility and Impact on nerve histology
Isolated Rat Vagal Nerve Preparation: Block and Recovery of Abdominal Vagus

$A_\delta: 2 mA < EC_{50} < 3 mA$

$C: 7 mA < EC_{50} < 7.5 mA$

Waataja et al. J Neural Eng 2011
CAP Recovery Post-block

- Electrode: Monopolar nerve cuff with Pt-Ir contact (humans, pigs), bipolar hook with Pt-Ir (rats)
- Waveform: 5 kHz charge-balanced square wave, 90µsec pulse width
- Typical Amplitudes: 1-8 mApp
- Preparation: Isolated rat vagus nerve (primarily)
- Outcome Measure: Compound action potential (typically)
- Onset observed? Not tested
- Prolonged effect (post HFAC)? Minutes of recovery
- Nerve fiber selectivity? Perhaps

Fast and slow waves of CAP blocked at 5000 Hz and 2-4 mA
CAP recovered to 50% by 2 min and 90% by 10 min

Tweden et al. Gastroenterology 2006;130:A148
Porcine Safety Models

Chronic 1-12 wk Safety Model (71 pigs, 142 leads)

- Placed electrodes on posterior and anterior vagal trunks at EGJ via laparotomy
- Applied vagal block for 5 min “on”/ 5 min “off” cycles for 24 hrs per day out to 12 weeks at up to 8 mA
- Evaluated:
  - Fibrous capsule formation between the electrode and the nerve (300µm at 12 wk)
  - Histologic response of the vagal fascicles and axons to the electrode and electrical algorithm
  - Maintenance of nerve function
  - Gross and histologic response of gastrointestinal organs
Histology Results

H&E, bar = 200 µm

T-blue, bar = 50 µm

E=electrode, FC= fibrous capsule, N=nerve fascicle
Representative Vagal Trunk Histopathology, Porcine Model, 90 days post-block

Control- vagus, 400x

Active- vagus, 200 - 400x

No evidence of necrosis, Wallerian degeneration, eosinophilic change/early axonal degeneration of the axons

Internal data
Testing Vagal Function

- Heart period change to deep breathing: 6 per min, normal for age and gender >10 / min
- Pancreatic polypeptide response to sham feeding

From Dr M Camilleri
Block and Recovery of Pancreas Porcine PES Model (n=6)

- Vagal block → PES ↓ > 80%
- Mean PES recovery 19±8 min

Tweden et al. Obesity Surgery 2006;16:988
Effect of Sham Feeding (SF) on Plasma PP During Fast

Methods

- 25 obese pts (age: 30-58 yrs; BMI: 33-48 kg/m²; 20 F, 5M)
- Sham feeding after 12 wks of VBLOC therapy
- 10 patients also had pre-implant SF
- Maestro RF1 System

Fast for 8 hrs overnight

![Graph showing VBLOC and sham feeding by chew and spit](Image)

Effect of VBLOC on weight loss

Camilleri et al. Surgery 2008;143:723-31
Prior data had established $\Delta$ plasma PP <25pg/ml = vagal inhibition

Camilleri et al. Surgery 2008;143:723-31
Greater Weight Loss in Patients with Suppression of PP on VBLOC

Plasma pancreatic polypeptide (pg/ml) vs % EWL

- Suppressed (<25, n=15)
- Non-suppressed (≥25, n=10)

Data mean + SEM

p=0.02

Camilleri et al. Surgery 2008;143:723-31
VBLOC Reduces Calorie Intake Without Changing Dietary Composition

![Graph showing calorie intake reduction across time points.](image)

*Each visit shows a significant reduction from baseline (all p=.02)

Camilleri et al. Surgery 2008; 143: 723-31
Wray et al. Obesity 2011; 19:5150
VBLOC Results in Early Fullness in MTV Study in Humans

Herrera et al. Gastroenterology 2009; 136: A-386
Weight loss during chronic, cervical vagus nerve stimulation in depressed patients with obesity: an observation

Effect of VNS on BMI

- normal
- overweight
- obese
- severe obese

Decrease in BMI (kg/m²) vs. BMI at baseline (kg/m²)

31, 1756–1759; online 12 June 2007