Analgesic Effects of Transcutaneous Vagus Nerve Stimulation (VNS) in Healthy Volunteers

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Impact of VNS on pain: Preclinical data

• Electrical VNS modulates nociception. Effects depend upon vagal input to NTS and subsequent relays such as NRM and LC.
  
  Randich & Gebhart Brain Res Rev 17: 77-99, 1992

• VNS activates the ascending antinociceptive pathway from PAG onto VPM and the descending antinociceptive system acting on STN.
  
  Nishikawa et al., Brain Res 833: 108-11, 1999

• VNS reduces duration of nociceptive behavior in the orofacial formalin pain model and the number of Fos-activated neurons in the STN.
  
  Bohotin et al., Pain 101: 3–12, 2003

• Decreased vagal activity by vagotomy aggravates both the severity and the time course of painful polyneuropathy.
  
Vagus Nerve Stimulation (VNS)
Impact of VNS on pain: Clinical data

• A prospective trial in drug-resistant epilepsy showed reduction of wind-up phenomenon and tonic pressure pain under invasive VNS.
  
  Kirchner et al., Neurology 55: 1167-71, 2000

• A retrospective study in epilepsy patients with VNS identified 10 migraineurs. Eight had a reduction of monthly frequency of ≥50%.
  
  Lenaerts et al., Cephalgia 28: 392-5, 2008

• Drug-resistant chronic cluster headache or migraine significantly improved in 4 out of 6 patients under invasive VNS.
  
  Mauskop, Cephalalgia 25: 82-6, 2005

• 5 out of 11 patients with fibromyalgia attained efficacy criteria with VNS. 2 patients no longer met widespread pain or tenderness criteria.
  
VNS – Mode of action

- Cervical branch of VN
- Surgical intervention
- Side effects: hoarseness, cough, pain, dyspnea, nausea

Cerebral activation

Brainstem projection

Site of stimulation
transcutaneous VNS (t-VNS)

Site of stimulation

Cerebral activation

Brainstem projection

Site of stimulation
transcutaneous VNS: Site of stimulation

A) ABVN exclusively supplies the cyma conchae.
   Peuker & Filler, Clin Anat 15: 35–7, 2002

B) Complete anesthesia of concha after section of vagus nerve.
   Fay, J Neurol Psychopathol 8: 110–23, 1927

C) Herpetic vesicles in concha due to herpes zoster of vagus nerve.
   Ohashi et al., Rinsho Shinkeigaku 34: 928–9, 1994

D) Auricular syncope triggered by mechanical stimulation of concha.
   Thakar et al., J Laryngol Otol 122: 1115–7, 2008

E) Referred otalgia with non-metastatic lung cancer.
   Eross et al., Cephalalgia 23: 2–5, 2003

F) Ear-cough reflex.
transcutaneous VNS (t-VNS)
**Hypothesis:** t-VNS alters pain perception in man

Two trials in healthy volunteers:

1. Randomized, crossover, two arms  
   n=48, left-sided t-VNS  
   complete quantitative sensory testing (QST) protocol

2. Randomized, controlled, crossover, three arms  
   n=49, left-sided and right-sided t-VNS  
   selected QST tests
Impact of t-VNS on pain: 1st trial

Study design

- 2 randomized sessions with active or sham t-VNS on different days
- Volunteers: n=48 (24♀, 24♂), 23.3±2.1 years
- Psychophysics: standard QST protocol plus tonic heat pain

![Diagram showing the experimental design](image-url)
Impact of t-VNS on pain: 1st trial

Results

• Pressure Pain Threshold (PPT): Stimulation × Side: p<0.05, F=4.6
• Mechanical Pain Threshold (MPT): Stimulation × Side p<0.01, F=7.7
• Mechanical Pain Sensitivity (MPS): Stimulation × Side p<0.05, F=6.6
• Tonic Heat Pain (THP): Stimulation p<0.001, F=14.3
Impact of t-VNS on pain: 1st trial

Results

• Pressure Pain Threshold (PPT): Stimulation × Side: p<0.05, F=4.6
• Mechanical Pain Threshold (MPT): Stimulation × Side p<0.01, F=7.7
• Mechanical Pain Sensitivity (MPS): Stimulation × Side p<0.05, F=6.6
• Tonic Heat Pain (THP): Stimulation p<0.001, F=14.3

• Thresholds of innocuous mechanical stimuli remained unchanged.
• Thermal thresholds remained unchanged.
Impact of t-VNS on pain: 1st trial

Summary and Conclusions

• PPT: Decrease of deep tissue pain.

• MPT, MPS: Decrease of nociception for mechanical pain stimuli.

• Selective effect on noxious parameters without any alteration of non-painful processing.

• Analgesic effects of t-VNS as shown by QST parameters PPT, MPT, and MPS. Evidence for lateralization on ipsilateral side.

• Reduced temporal summation of noxious tonic heat on both sides.
Impact of t-VNS on pain: 2nd trial

Study design

• 3 randomized sessions with active or sham t-VNS on different days
• Volunteers: n=49 (25 ♀, 24 ♂), 23.4±4.2 years
• QST parameter: PPT, MPT, MPS
Impact of t-VNS on pain: 2nd trial

Results

- Pressure Pain Threshold (PPT)

\[ p<0.05, F=4.3, n=94 \]
Impact of t-VNS on pain: 2\textsuperscript{nd} trial

Results

• Mechanical Pain Threshold (MPT)

\[ p<0.05, F=4.0, n=96 \]
Impact of t-VNS on pain: 2\textsuperscript{nd} trial

Results

• Mechanical Pain Sensitivity (MPS)

\[ p=0.06, F=2.8, n=92 \]
Impact of t-VNS on pain: 2\textsuperscript{nd} trial

Summary and Conclusions

• PPT: Decrease of deep tissue pain processing on both sides.
• MPT: Decrease of nociception for mechanical pain stimuli on both sides.
• MPS: Tendency to reduction.
• No indication of lateralized analgesic effect of t-VNS.
Impact of t-VNS on pain: Clinical trials

- Evoked pain analgesia in chronic pelvic pain patients using respiratory-gated auricular vagal afferent nerve stimulation
  - 15 patients with chronic pelvic pain due to endometriosis
  - Invasive auricular stimulation at left cymba conchae or ear lobe

- Transcutaneous vagus nerve stimulation for the treatment of chronic migraine
  German Clinical Trials Register: DRKS00003681
  - Randomized controlled trial in 98 patients with chronic migraine
  - Transcutaneous VNS of the left cymba conchae
Transcutaneous Vagus Nerve Stimulation

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