Title: Adjunctive non-invasive vagus nerve stimulation helps to reduce symptoms of mild traumatic brain injury

Mild traumatic brain injury (mTBI), also known as concussion, is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits. Non-invasive vagus nerve stimulation (nVNS) has been shown to improve cognitive function, reduce inflammation, reduce breakdown of the blood-brain barrier, has neuroprotective effects, and balances the autonomic system. Due to these mechanisms, nVNS has recently been suggested as a potential adjunctive therapy for mTBI.

METHODS: Data collection took place at Cherry Creek Neurology from October 2020 to September 2024. Patient selection for use of adjunctive nVNS was based on clinical diagnosis of mTBI (based on history), examination by a neurologist, elevated Neurobehavioral Symptom Inventory (NSI) score and patient willingness to engage in the trial. NSI was completed at baseline (NSI1) and approximately 3 months after starting nVNS (NSI2). Additional surveys to evaluate PTSD, depression, and anxiety were also collected. Patients were concurrently managed with standard of care, taken in context with each individual patient and circumstance. Patients were prescribed nVNS and were instructed to deliver two consecutive stimulations, twice per day. NSI1 and NSI2 scores were compared using the Mann-Whitney Test. Correlation coefficients were measured between NSI scores as well as PTSD, depression, and anxiety health surveys. The effect of injury date on severity of baseline scores and magnitude of change was tested with ANOVA.

RESULTS: 175 patients were evaluated, of which 102 had complete data. The time since injury to the NSI1 baseline ranged from 5 days to 3.5 years. Results showed that adjunctive nVNS significantly reduced NSI scores from baseline in mTBI patients. Twenty-two of 27 NSI components showed significant improvement ($p<0.05$). NSI components that showed the most significant changes were headache (-0.79, $p = 2.1 \times 10^{-7}$), concentration (-0.59, $p = 0.0002$), total NSI score (-9.72, $p = 0.0003$), and affective score (-3.23, $p = 0.0004$). NSI components that showed the greatest fractional change from baseline were headache (-23.2%), nausea (-23.0%), total score (-16.4%), dizziness (-15.1%), and depression (-13.8%). Strong negative correlations were measured between NSI1 severity scores and total magnitude of change with the strongest negative correlation found between the initial NSI1 score and change in score for 'loss of balance' ($r = -0.66$). There were notable correlations between the NSI1 score for "depression" and health surveys measuring anxiety (GAD7, $r = 0.60$) and depression (PHQ9, $r= 0.66$). Time since injury did not show a significant effect when looking at the total magnitude of change in NSI scores.

CONCLUSION: When added to standard of care nVNS was associated with reduced symptoms resulting from mild traumatic brain injury including post-traumatic headache, poor concentration, and nausea, regardless of the time since injury to start of treatment.

Adjunctive Non-invasive Vagus Nerve Stimulation Helps to Reduce Symptoms of Mild Traumatic Brain Injury

CHERRY CREEK NEUROLOGY

If you would like to discuss this work, please email.

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Introduction

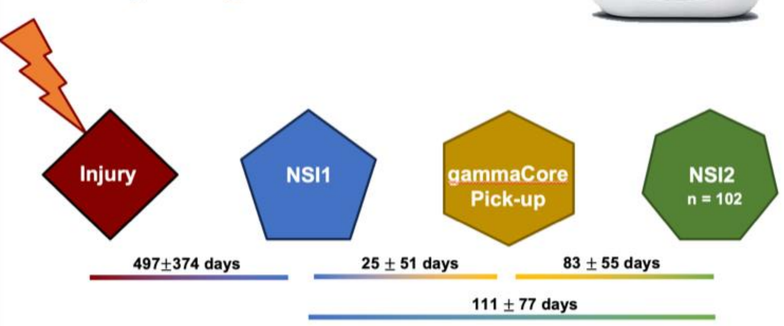
Mild traumatic brain injury (mTBI), also known as concussion, is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits. Non-invasive vagus nerve stimulation (nVNS) has been shown to improve cognitive function, reduce inflammation, reduce breakdown of the blood-brain barrier, has neuroprotective effects, and balances the autonomic system. Due to these mechanisms, nVNS has recently been suggested as a potential adjunctive therapy for mTBI.

Methods

Data collection took place at Cherry Creek Neurology from October 2020 to September 2024. Patient selection for use of adjunctive nVNS was based on clinical diagnosis of mTBI (based on history), examination by a neurologist, elevated Neurobehavioral Symptom Inventory (NSI) score and patient willingness to engage in the trial. NSI was completed at baseline (NSI1) and approximately 3 months after starting nVNS (NSI2). Additional surveys to evaluate PTSD, depression, and anxiety were also collected. Patients were concurrently managed with standard of care, taken in context with each individual patient and circumstance.

Patients were prescribed nVNS and were instructed to deliver two consecutive stimulations, twice per day, using the **gammaCore™ device developed by electoCore.**

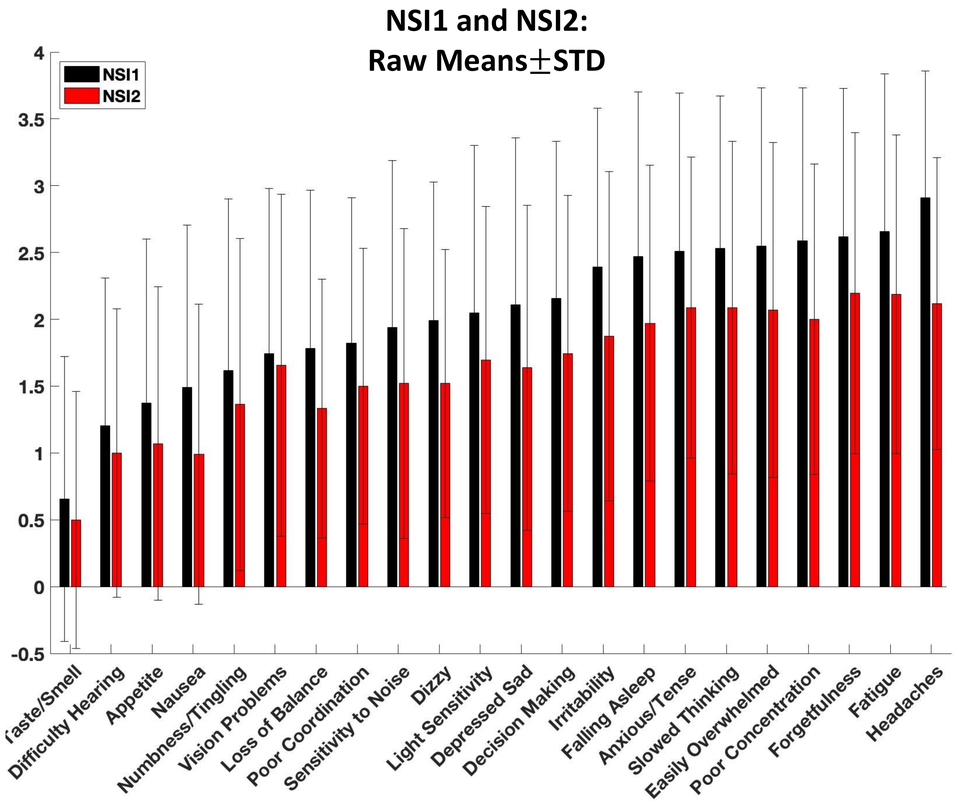
Study Design



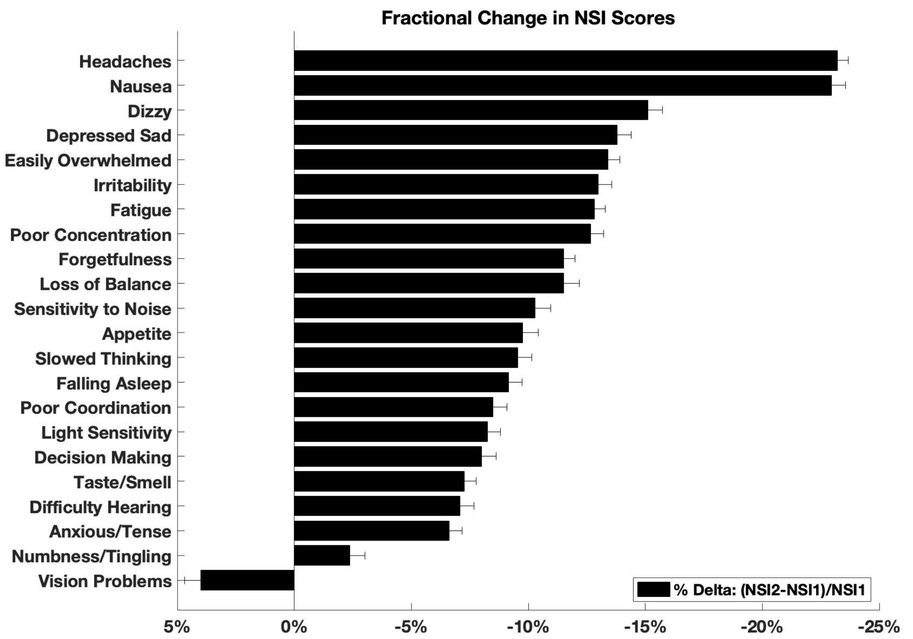
NSI1 and NSI2 scores were compared using the Mann-Whitney Test. Correlation coefficients were measured between NSI scores as well as PTSD, depression, and anxiety health surveys. The effect of injury date on severity of baseline scores and magnitude of change was tested with ANOVA. **175 patients were evaluated, of which 102 had complete data. The time since injury to the NSI1 baseline ranged from 5 days to 3.5 years**.

Results

Adjunctive nVNS significantly reduced 23 of 27 NSI parameters from their baseline values in mTBI patients.

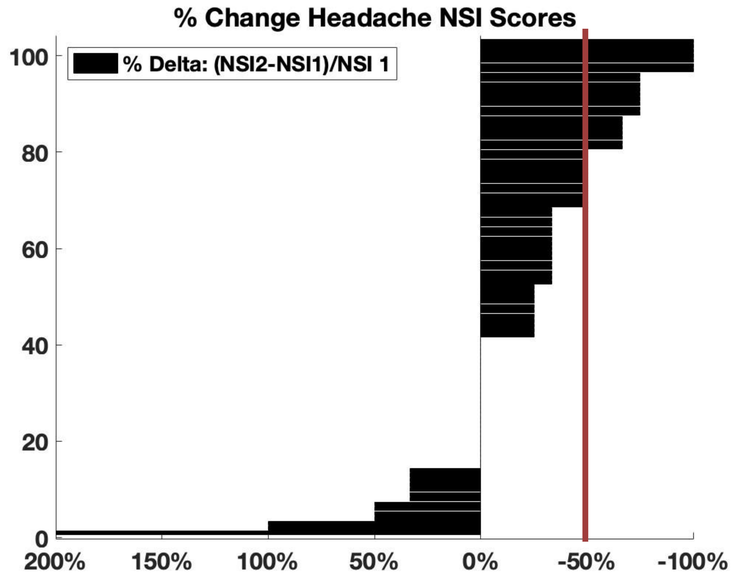


Twenty-three of 27 NSI components showed significant improvement ($p<0.05$). NSI components that showed the most significant changes were **headache** (-0.79, p = 2.1x10-7), **concentration** (-0.59, p = 0.0002), **total NSI score** (-9.72, p = 0.0003, not shown), and **affective score** (-3.23, p = 0.0004, not shown).



- NSI components that showed the greatest fractional change from baseline were **headache** (-23.2%), **nausea** (-23.0%), **total score** (-16.4%, not shown), **dizziness** (-15.1%), and **depression** (-13.8%). Means±STD

- **Strong negative correlations** were measured between NSI1 severity scores and total magnitude of change with the strongest negative correlation found between the initial NSI1 score and change in score for 'loss of balance' (r = -0.66).
- There were **notable correlations** between the NSI1 score for "depression" and health surveys measuring anxiety (GAD7, r = 0.60) and depression (PHQ9, r= 0.66).



When looking at changes in NSI scores across individual patients, **33% of patients experienced a 50% or greater improvement** in their **headache symptoms**.

- Except for NSI: Appetite (p = 0.47)**, the **initial severity of symptoms was similar regardless of injury date** (ANOVA; 'Numbness' p = 0.11 to 'Taste/Smell' p = 0. 94). **Scheffe's Post-hoc analysis for 'Appetite' showed no difference between group means.

- There was **no effect** on the percentage of symptom improvement when considering injury date (ANOVA; 'Fatigue' p = 0.09 to 'Noise Sensitivity' p = 0. 97)

Conclusions

When added to standard of care nVNS was associated with reduced symptoms resulting from mild traumatic brain injury including post-traumatic headache, poor concentration, and nausea.

Date of injury vs Initial Severity (NSI1)

- There was no difference in initial symptom severity whether the patient was injured 3 months or 2 years prior to baseline testing.

Date of injury vs Symptom Improvement

- There was no difference in degree of symptom improvement with adjunctive nVNS whether the patient was injured 3 months or 2 years prior to treatment.

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