

Experimental research

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VAGUS NERVE STIMULATION MODULATES THE CRANIAL TRIGEMINAL-AUTONOMIC REFLEX – A COMPARISON TRIAL OF DIFFERENT SHAM-CONDITIONS.

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Introduction: Non-invasive vagal nerve stimulation (nVNS) has been proposed as a novel treatment for migraine and cluster-headache patients (1-3). Cranial autonomic symptoms such as lacrimation and conjunctival injection are characteristic features in some primary headache disorders (4). Recently, we were able to show that nVNS modulates the trigeminal autonomic reflex in healthy participants. However, a study, using nVNS in order to treat cluster headache attacks, failed to find overall group effects between nVNS and sham treatment as responses to sham treatment were noticeably high (5).

Objectives: The purpose of this study was to compare the effects of nVNS (electroCore stimulation device) on the trigeminal-autonomic reflex with sham nVNS (as used in clinical studies), no stimulation and verum stimulation at the back of the neck.

Methods: 28 healthy participants (15 female, 13 male, mean \pm SD age= 26.29 \pm 4.57) were recruited and participated in a single-blind, within-subject design. The four different conditions (i) no stimulation, (ii) verum stimulation of the posterior neck, (iii) electroCore sham stimulation and (iv) regular nVNS were applied in a pseudorandomized order for 3 x 2 minutes. Lacrimation, as a quantifiable physiological autonomic output, was subsequently provoked using kinetic oscillation stimulation (KOS) (Chordate Medical AB, Stockholm, Sweden) of the nasal mucosa (6) and quantified using a Schirmer's II test before the stimulation (baseline), as well as during the KOS procedure. As an indicator of autonomic activation, the mean difference between lacrimation at baseline and lacrimation after one minute of KOS was calculated.

Results: The regular nVNS treatment resulted in a significant reduction of ipsilateral KOS-induced lacrimation compared to no stimulation ($p=0.003$) and stimulation of the posterior neck ($p=0.02$). Surprisingly the same effect was observed after stimulation with the electroCore sham device ($p=0.003$; $p=0.001$). There was no significant difference between nVNS and stimulation with the electroCore sham device.

Conclusion: KOS-induced lacrimation was significantly reduced after regular nVNS stimulation compared to no stimulation and stimulation of the posterior neck. However, after stimulation with the electroCore sham device the lacrimation was also significantly reduced. These data suggest that regular nVNS and the sham device used in randomized trials activate the vagal system and only stimulation of the posterior neck may be considered a true sham for regular nVNS stimulation.

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