# Effect of Interactive Neurostimulation Therapy on Inflammatory Response in Patients With Chronic and Recurrent Mechanical Neck Pain

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## Abstract

**Objective:** The purpose of this study is to evaluate the effect of treatment with a novel noninvasive interactive neurostimulation device (InterX5000) on the production of inflammatory biomarkers in chronic and recurrent mechanical neck pain (NP) syndrome.

**Methods:** This study represents pilot biological data from a randomized controlled clinical trial. Twenty-five NP patients and 14 asymptomatic subjects included for baseline comparison only completed the study. The patients received 6 InterX5000 or placebo treatments within 2 weeks, and pretreatment and post-treatment blood samples were collected for in vitro determination of biomarker production. Whole blood cell cultures were activated by lipopolysaccharide or by the combination of lipopolysaccharide and phytohemagglutinin for 24 to 48 hours. The levels of tumor necrosis factor α (TNFα) and its soluble type II receptor (sTNFR II), interleukin (IL) 1, IL-1 receptor antagonist (IL-1RA), IL-6, IL-10, and monocyte chemotactic protein (CCL2/MCP-1) were determined by specific immunoassays.

**Results:** Compared with asymptomatic subjects, baseline production levels of all proinflammatory mediators (TNFα, IL-1β, IL-6, and CCL2/MCP-1) were significantly augmented or trended higher ($P$ = .000-.008) in patients with NP. Of the anti-inflammatory markers, only IL-1RA was significantly elevated ($P$ = .004). The increase in IL-10 and tumor necrosis factor receptor II levels did not reach statistical significance. Neither InterX5000 nor placebo therapy had any significant effect on the production of the inflammatory mediators over the study period.

**Conclusion:** This investigation determined that inflammatory cytokine pathways are activated in NP patients but found no evidence that a short course of InterX5000 treatment normalized the production of inflammatory biomarkers. (J Manipulative Physiol Ther 2015;xx:1-10)

**Key Indexing Terms:** *Neck Pain; Electrotherapy; Inflammation; Cytokines*

The primary objective in the treatment of patients with uncomplicated chronic and recurrent mechanical neck pain (NP) is pain reduction and restoration of cervical mobility. The management of NP often involves a multidisciplinary and multimodal approach including traditional medical as well as conservative interventions such as physiotherapy, chiropractic, massage, and acupuncture. Electrotherapy is a modality that is commonly used by physiotherapists and chiropractors. Although some forms of electrotherapy have been reported to provide analgesic effects, no consensus exists currently as to their clinical benefits for the treatment of cervical pain [1,2]

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In recent years, several clinical studies have reported on the hypoalgesic effect of a relatively new form of electrotherapy based on the application of noninvasive interactive neurostimulation (NIN) generally delivered through a device trademarked InterX. The manufacturer purports that the device works by locating areas of low skin impedance, which generally "relate to major nerve branches, trigger points, acupuncture points and localized areas of sympathetic skin response."[3] The analgesic effects of InterX have been attributed to a distinctive electrode positioning as well as higher amplitude and density of the applied current, compared with transcutaneous electrical nerve stimulation (TENS).[3,4] To date, 3 randomized controlled clinical trials using different models of InterX have shown advantage of this modality over placebo application in postoperative recovery from bone fractures,[4] knee replacement surgery,[5] and ankle fracture.[6] Interestingly, in a recent study, Schabrun et al[7] have shown that interactive neurostimulation therapy (NIN) may be also efficacious for managing musculoskeletal conditions, such as myofascial pain syndrome, and be of clinical significance in some patients with shoulder or NP.

Although the underlying pathophysiology of NP is considered to be multifactorial and remains to be fully elucidated, experimental and clinical reports suggest that mechanical NP is associated with a local inflammatory response.[8,9]

Inflammatory markers including tumor necrosis factor α (TNFα) and nitric oxide as well as 2 chemotactic chemokines, macrophage chemotactic protein 1 (CCL2/MCP-1) and macrophage inflammatory protein 1 (CCL3/MIP-1α) have been shown to be consistently elevated in such patients, both in vitro and in vivo.[10] Thus, it appears that NP patients demonstrate up-regulation of inflammatory mediator pathways and thereby could potentially benefit from therapies targeting the local inflammatory response.

Biological mechanisms underpinning the effects of NIN through the application of InterX have not been explored. However, the existing clinical reports suggest that NIN may exert an anti-inflammatory effect in the area of local inflammation.[5,6] The present study was undertaken to investigate if the InterX$^{T}$5000 therapy, independent of other therapeutic interventions, might attenuate/normalize the production of inflammatory mediators in NP patients. Objective measures of pain and function were done immediately pre-InterX5000 and post-InterX5000 therapy.

## Methods

### Patients

All subject-handling procedures and the informed consent form were approved by the Canadian Memorial Chiropractic College Research Ethics Board. The trial was registered with clinicaltrials.gov (NCT01382537). Of 49 patients recruited, 41 met the inclusion criteria to participate in this randomized controlled intervention trial. Fourteen asymptomatic control subjects were also included for baseline comparison (Fig 1).

***Inclusion/Exclusion Criteria.*** Subjects (21-65 years of age) were enrolled in the study based on their presentation for treatment of chronic and recurrent mechanical NP, with or without referral to the shoulder or upper arm. *Chronicity* was defined as persistence of symptoms for 3 months duration. Patients with history or examination findings suggestive of herniated disc or stenosis (neural stretch signs, arm pain aggravated by head movement, muscular weakness, dermatomal hypersensitivity, or change in motor reflexes) and a history of fracture or surgery to the neck or shoulder were excluded from the study. In addition, patients with a history of phlebitis, recent (within 3 months) use of chemotherapy or radiation therapy, cortisone treatment (within 30 days), or Botox use (within 3 months) were also excluded. Control (asymptomatic) subjects met the same criteria but were without any neck or shoulder pain within at least the past 3 months. Candidates with history of any type of electrotherapy treatment anywhere on the body within the previous 6 months also were excluded.

### Treatment With InterX5000

*Treatment Intervention.* Subjects were randomly allocated to 1 of 2 treatment groups (Fig 1): active stimulation (AS) or control stimulation (CS) (ie, placebo treatment). Allocation was concealed using sealed envelopes. The mean pretreatment pain level measured on a 100-point visual analog scale (VAS) was 47.6 ± 25.3 and 37.2 ± 18.1 for the AS and CS groups, respectively. The pretreatment neck disability index (NDI) for the AS group was 25.5 ± 14.4 and for the CS group 27.3 ± 12.8 (Table 1). *Treatment frequency* was defined as 3 sessions per week, occurring on consecutive days in week 1 and on alternate days, for week 2. Patients were eliminated from the study and replaced if they received any other form of therapy or medication for NP during the treatment interval.

The treatment protocols were standardized based on common utilization recommendations from the manufacturer. Patient information and instructions given as treatment was administered were designed to conceal treatment group allocation. An exit interview was used to determine the extent to which unblinding occurred.

Each treatment session lasted 25 minutes. For the CS group, the information on therapeutic dosage of stimulation was given as being the level of stimulus just below that which can be perceived by the patient. The handheld stimulation unit was applied to the skin of the trapezial shoulder region, and the voltage amplitude increased to a level the subject indicated as perceptible. The subject was then asked to indicate when the sensation was no longer detectable as the amplitude was gradually turned down. On signal from the subject that sensation had ceased, the unit was turned to "0" for the treatment. In the AS group, the instructions defined the therapeutic dosage to be just above the threshold necessary for perception of the stimulus. As the signal was ramped up, the