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;38:545-554)

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

subject verbalized when it was perceived, and then the stimulus was increased noticeably to its final position for the treatment. The location of the controls and meter on the handheld unit prevented visualization by the subject, and each unit was equipped with a buzzer providing equivalent auditory background noise during treatment. Treatment consisted of 5 minute sweeping motion across the skin from the occipital base radiating outward across the distribution of the upper trapezius. This was followed by focused treatment at 5 sites, 3 on the more symptomatic side of the neck and 2 on the opposite side, each treatment consisting of 4 minutes. For the CS group, the locations were standardized as midcervical, interscapular adjacent to the medial angle of the scapula and mid supraspinatous sites ipsilaterally and 2 of the same 3 sites contralateral to the more painful side. For the AS group, the 3 sites most sensitive to the sweeping scan, identified with the InterX5000 device, were on the more symptomatic side and 2 on the opposite side. Generally, these sites were approximately the same as those standardized for the CS group. Finally, during treatment, patients volitionally stretched the neck muscles under provider guidance while stimulation continued.

Laboratory Studies

Blood Collection. Heparinized peripheral blood samples (3 in total, 5 mL each) were collected by venipuncture from the antecubital fossa area of the arm. A baseline sample was collected before any therapeutic intervention, and 2 subsequent samples were collected immediately following the third and sixth treatment with InterX5000 (for laboratory assessments designated test 1 and test 2, respectively). Samples from healthy asymptomatic controls were obtained in an identical manner. All samples were transferred to the laboratory and processed within 60 minutes of collection.

Culture System. Blood samples were diluted 10-fold with tissue culture medium (RPMI 1640, GIBCO; Invitrogen, Grand Island, NY) supplemented with 5×10^{-5} mol/L of 2-mercaptoethanol, L-glutamine, and antibiotics. Duplicate whole blood (WB) cultures, from patients and control subjects, were prepared essentially as described previously.[11] Cultures were maintained for 24 or 48 hours at 37°C, in a humidified 5% CO_2 incubator. At the conclusion of the incubation period, culture supernatants from each subject were pooled, centrifuged to remove any contaminating cellular material, aliquoted, and frozen at −78°C until further analysis.

Constitutive (Spontaneous) and Inducer-Related Mediator Production. Inflammatory biomarker determinations included the pro-inflammatory markers TNFα, interleukin (IL) 1β (IL-1β), IL-6, CCL2/MCP-1, and the anti-inflammatory mediators IL-1 receptor antagonist (IL-1RA), soluble tumor necrosis factor receptor II (sTNFR II), and IL-10.

To induce TNFα, IL-1β, IL-1RA, and IL-6 production, WB cultures were stimulated for 24 hours with lipopolysaccharide (LPS) from *Escherichia coli* serotype 055:B5 (Sigma-Aldrich, St Louis, MO) at a concentration of 1 μg/mL. Inducer-related production of CCL2/MCP-1, IL-10, and sTNFR II were studied in WB cultures stimulated for 48 hours by the combination of LPS (1 μg/mL) and phytohemagglutinin (PHA; Sigma-Aldrich) at 10 μg/mL. To determine background (ie, constitutive) levels of synthesis of each mediator studied, parallel preparations were cultivated in the absence of the stimulant.

Determination of Mediator Levels. The levels of the studied mediators were determined by specific enzyme-linked immunosorbent assays (ELISA) using DuoSet ELISA development system for natural and recombinant human cytokines and soluble cytokine receptors (R&D Systems, Minneapolis, MN) according to the manufacturer's recommendations. Each of the studied culture supernatants was tested a minimum of 3 times at 2 to 4 different dilutions.

Statistics

The data for this investigation represent a pilot subset of data from a randomized clinical trial. The larger clinical trial (n = 80, with 40 subjects required from each of 2 participating centers) was powered considering a medium effect size, with 80% power on the clinical outcomes.[12] After randomization at the first (present) center (n = 49), a pilot sample of 25 available subjects (n = 13 allocated to the intervention and n = 12 allocated to the placebo) was provided for the current investigation. To this pilot sample, an additional 14 subjects meeting all requirements for asymptomatic controls were included for comparison purposes (Fig 1).

Primary outcome for the study was defined as the within patient difference in inflammatory mediator level between baseline, determined at the time of NP patient enrollment into the study, and that measured after 3 and 6 applications of InterX5000 treatments. Between-group comparisons included evaluation of differences in constitutive and inducer-related mediator levels between NP patients and asymptomatic controls. All outcome measures were evaluated for normality. Those measures meeting the appropriate assumptions for normality were analyzed using analysis of variance and *t* tests (including post hoc Bonferroni testing). Those not meeting the normality assumptions were evaluated using nonparametric tests (Kruskal-Wallis and Mann-Whitney *U* tests). Finally, a difference in proportions test was used to evaluate the responses on exit interview as to subject perception of treatment group allocation.

Because of the number of statistical tests conducted, the *P* value for significance was adjusted to .004. Those analyses yielding *P* values of less than or equal to .01 have been considered as trends. In addition, descriptive results were calculated for all measures. These results have been depicted graphically as means, ± 1 SE.

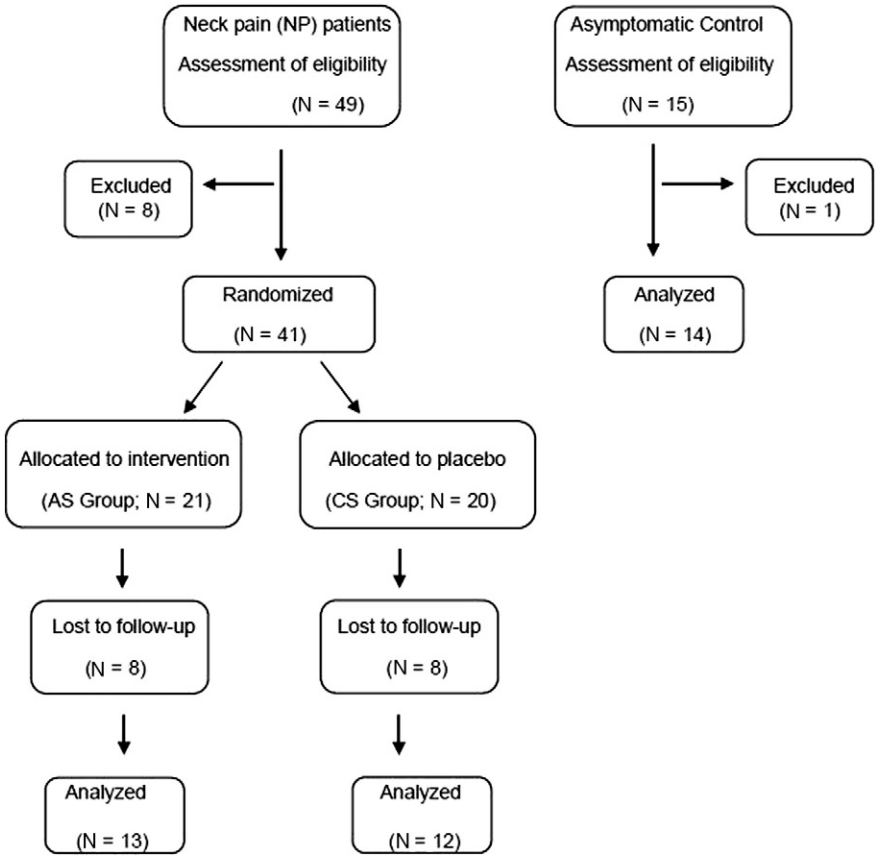

Fig 1. *Flow diagram of subjects through the study. AS group, active stimulation group; CS group, control stimulation group.*

Table 1. *Demographic Characteristics and Self-Reported Outcomes of Participants Before and After Completion of the Treatment Regimen (6 Treatments)*

Group	Age (y)	Sex (F/M)	VAS [a]		NDI [b]	
			Admission	End of Study	Admission	End of Study
NP patients (AS) (n = 13)	41.2 ± 14	6/7	46.6 ± 25.3	15.1 ± 24.8	25.5 ± 14.4	9.4 ± 18.4
NP patients (CS) (n = 12)	39.3 ± 15	9/3	37.2 ± 18.1	16.5 ± 22.8	27.3 ± 12.8	10.9 ± 10.1
Asymptomatic	33.4 ± 13	6/8	N/A			N/A

NDI, neck disability index; *N/A*, not applicable; *NP*, neck pain; *VAS*, visual analog scale.
[a] Visual analog scale (0-100 mm).
[b] Neck disability index (score/50).

Results

Of 41 NP patients enrolled, 25 completed the study (Fig 1) Post-treatment values obtained for VAS scores revealed substantial reductions both in the AS and CS groups (46.7 vs 15.5 and 37.1 vs 16.5) (Table 1). The magnitude of this effect was comparable in both groups and not significantly different between the AS and CS groups ($P = .38$). Similarly, there were no significant ($P = .98$) post-treatment differences in NDI scores between the AS and CS groups, although NDI scores in each of the study groups were markedly reduced (25.5 vs 9.4 and 27.3 vs 10.9) (Table 1).

The effect of InterX application on the production of 4 proinflammatory and 3 anti-inflammatory mediators in patients with NP included measurements of production of TNFα, IL-1β, IL-6, MCP-1 and IL-1RA, sTNFR II, and IL-10, respectively. Figures 2 to 6 and Table 2 depict the levels of synthesis of the indicated mediators in unstimulated and/or mitogen-stimulated WB cultures established from NP patients following 3 (test 1) and 6 (test 2) treatments with InterX5000 or placebo neurostimulation. The amounts of the biological material required for the completion of the study were limited. Thus, the assessments of the spontaneous (constitutive) production of TNFα, IL-1, and IL-6 were not carried out. Furthermore, our preliminary tests have established that levels of these cytokines generally remain below the detection level by DuoSet ELISA kits.

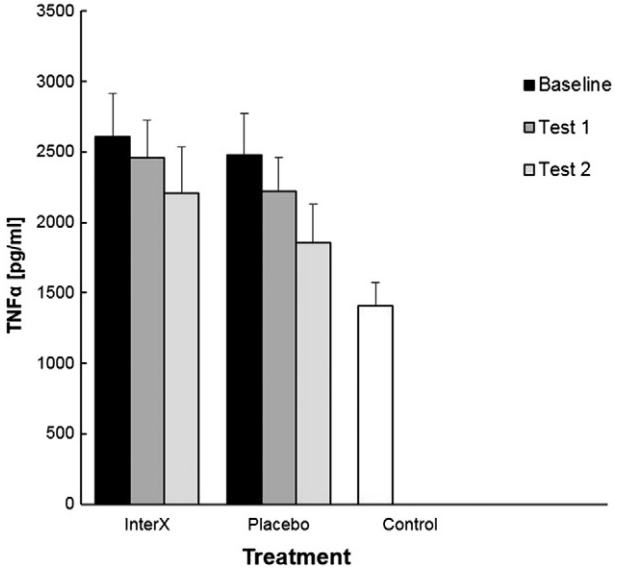

Fig 2. *The levels of LPS-induced TNFα production in WB cultures from patients with NP at baseline (time of admission into the study) and after 3 (test 1) and 6 (test 2) InterX 5000 or placebo treatments and from asymptomatic controls. Synthesis of TNFα was determined in tissue culture supernatants from LPS-stimulated WB cultures. The bars represent the mean values (±SEM) of TNFα production after 24-hour culture period. TNF, tumor necrosis factor.*

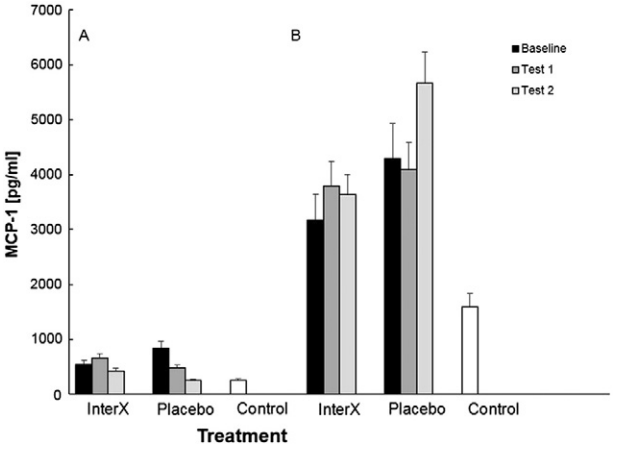

Fig 3. *The levels of constitutive (A) and LPS/PHA-induced (B) release of MCP-1 in WB cultures from patients with NP at baseline (time of admission into the study) and after 3 (test 1) and 6 (test 2) InterX5000 or placebo treatments and in WB cultures from asymptomatic controls. The levels of MCP-1 synthesis were determined in tissue culture supernatants from WB cultivated without (A) or in the presence (B) of the inducer for 48 hours. MCP, monocyte chemotactic protein.*

Inflammatory Mediator Production After Application of InterX5000

a) *TNFα, IL-1, and IL-6*. At the time of admission into the study, the in vitro production of all 3 proinflammatory cytokines (TNFα, IL-1, and IL-6) in LPS-stimulated WB cultures from NP patients were either significantly elevated or trended higher ($P = .002$, $P = .000$, and $P = .008$, respectively) compared with that in asymptomatic subjects (Fig 2; Table 2). Compared with their respective baselines, a slight decline in response to LPS stimulation in tests 1 (after 3 treatments) and 2 (after 6 treatments) was apparent in both study groups (InterX5000 and placebo). However, the magnitude of the observed decreases was comparable in both groups and, therefore, not likely to be related to the InterX5000 therapy the patients received.

b) *MCP-1*. Figure 3 illustrates the changes in the level of production of MCP-1 in unstimulated (A) and LPS-/PHA-stimulated (B) cultures from the InterX5000 and placebo-treated NP patients. The baseline production of this chemokine was significantly ($P < .001$) elevated in NP patients compared with the asymptomatic control in the mitogen-activated (Fig 3B) WB cultures. While the constitutive synthesis of MCP-1 in unstimulated WB cultures from the InterX5000-treated group remained higher than in the asymptomatic control, the placebo-treated subjects normalized the spontaneous release of this mediator to the control level (Fig 3A). On the other hand, no significant changes in the level of MCP-1 synthesis were observed in mitogen-activated preparations from InterX5000 patients examined after 3 and 6 treatments with either form of therapy. The production of this chemokine increased further, although not significantly compared with the baseline level, in the placebo-treated patients (Fig 3B).

Anti-Inflammatory Mediator Production After Application of InterX5000

a) *sTNFR II and IL-1RA*. As the levels of both TNFα and IL-1RA synthesis were consistently and significantly elevated in the studied patients, we examined the magnitude of the production of the natural inhibitors of their activity, sTNFR II and IL-1RA (Figs 4A and B and 5A and B). Compared with the asymptomatic control, the baseline levels of the mitogen (LPS/PHA combination)–stimulated release of sTNFR II were elevated in NP patients ($P = .002$). However, at both study times, InterX5000 and placebo treatments had no significant effect on the production of this molecule regardless of the culture conditions (Fig 4A and B).

In contrast to sTNFR II, the baseline synthesis of IL-1RA in unstimulated as well as LPS-stimulated WB cultures from NP patients was elevated ($P = .003$ and $P = .008$, respectively) compared with values in asymptomatic subjects (Fig 5A and B). No effect of either InterX5000 or placebo treatment was observed throughout the period of therapy, and only slight fluctuations in the level of spontaneous release of IL-1RA were noted in both groups of NP patients.

b) *IL-10*. Evaluation of the IL-10 production was carried out in cultures activated by the combination of LPS and PHA and assessed after a 48-hour incubation period. Baseline production of this cytokine in WB cultures from NP patients appeared

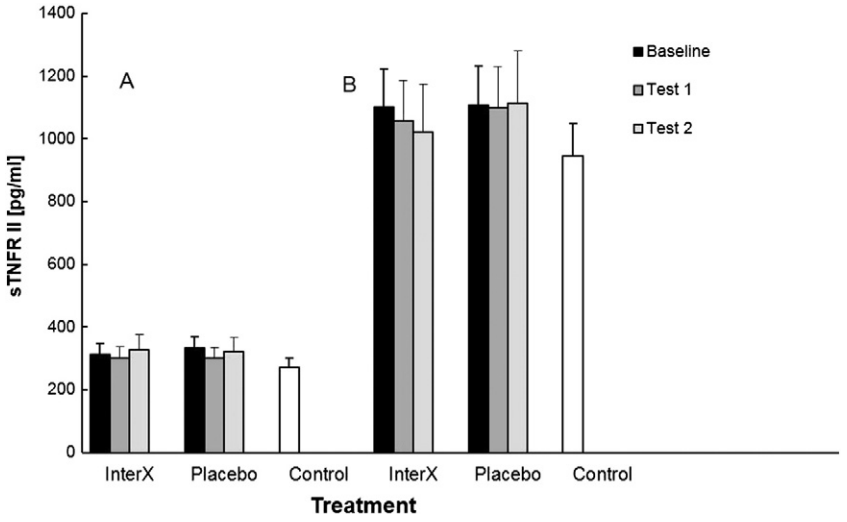

Fig 4. *Constitutive (A) and LPS-induced (B) production of sTNFR II in WB cultures from patients with NP after 3 (test 1) and 6 (test 2) InterX5000 or placebo treatments and in cultures from asymptomatic subjects (control). Whole blood cultures were cultivated in the absence (A) or presence (B) of LPS for 24 hours.*

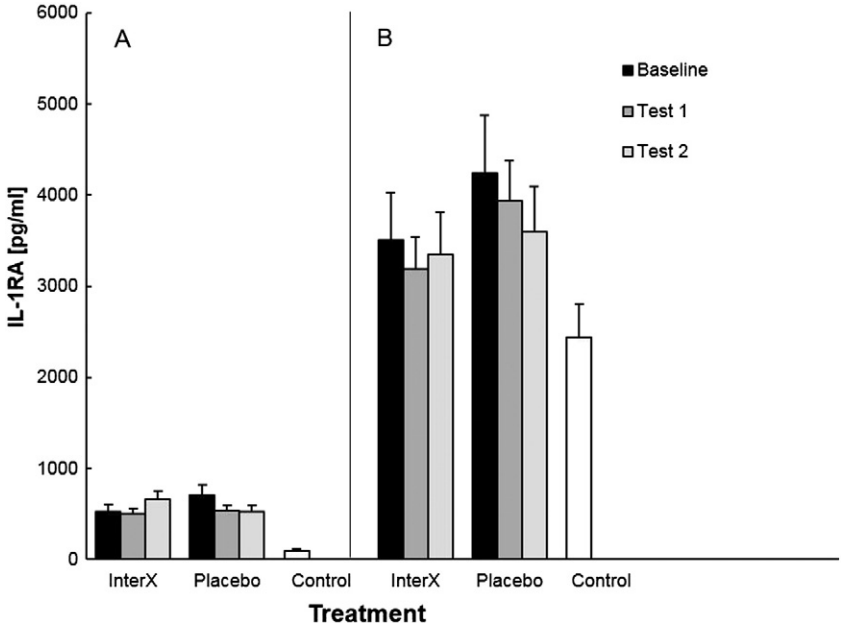

Fig 5. *Secretion of IL-1RA in unstimulated (A) and in LPS-activated (B) cultures from patients with NP after the regimen of 3 (test 1) and 6 (test 2) InterX5000 or placebo treatments and in cultures from asymptomatic control subjects. Whole blood cultures from the studied NP patients and asymptomatic controls were maintained for 24 hours in the absence (A) or presence (B) of LPS.*

to be somewhat higher than those from asymptomatic subjects (P = .069) (Fig 6). At both study times, InterX5000 and placebo treatments had no significant effect on the level of IL-10 production.

Exit Interview. Of the entire patient cohort, 52% were allocated to the AS group, and 48%, to the CS group. Upon exit interview with each subject, they were asked to indicate their belief as to the group to which they were allocated. Three-quarters of subjects reported that they had been assigned to the AS with the remainder thinking they were in the CS group ($Z = 2.086$; $P < .037$).

Discussion

The principle finding of this investigation is that the production of biological markers of inflammation in WB

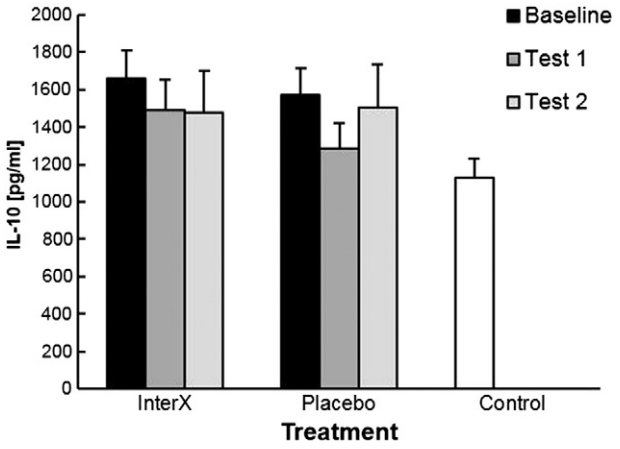

Fig 6. *Levels of IL-10 production in LPS/PHA -stimulated WB cultures from patients with NP who received 3 (test 1) and 6 (test 2) InterX5000 or placebo treatments and from asymptomatic controls. The production of IL-10 was determined in TC supernatants following 48 hours cultivation in the presence of the inducer. IL, interleukin.*

cultures from NP patients did not change after the application of NIN using the InterX5000 compared to placebo control patients. This was consistent with the clinical outcomes as indicated by the VAS and NDI data (Table 1).

Baseline data on inflammatory markers obtained in the present study confirm and expand on earlier observations of increased production of proinflammatory markers reported in blood cultures from patients with chronic NP.[10] Compared with asymptomatic subjects, constitutive and induced levels of proinflammatory mediator (TNFα, IL-1β, IL-6, and MCP-1) production were significantly augmented and trended high (Figs 2 and 3 and Table 2, respectively), as did the production of the anti-inflammatory mediator IL-1RA (Fig 5A and B). The synthesis of sTNFR II was also significantly increased (Fig 4). To our knowledge, anti-inflammatory mediator production in patients with cervical pain has not been investigated previously. Significantly augmented production of IL-1RA as well as increased production of tumor necrosis factor receptor II and potential increase in IL-10 reported herein has been typically associated with inflammatory conditions.[13-16] Thus, these data not only provide further confirmation of the sustained activation of inflammatory cytokine pathways in NP syndrome[10] but also present evidence of the disturbed balance between the production of proinflammatory cytokines and the natural inhibitors of their biologic activity.

Our search of the literature did not reveal any conclusive reports assessing the effects of various models of InterX directly on the mediators of the inflammatory response. Using frozen lymphocytes from 4 healthy subjects, Pyne-Geithman and Clark[17,18] reported, in conference proceedings, that the intracellular levels of proinflammatory cytokines were altered within 10 minutes post–InterX application. Other work has demonstrated beneficial effects of InterX application in acute postoperative cases, in terms of reduced edema in ankle fracture,[6] and attenuation of pain during recovery from bone fracture[4] and after knee replacement surgery.[5] These postsurgical studies suggest that the application of interactive neurostimulation may have a dampening effect on inflammation thereby providing some credence to the claim that InterX application may be beneficial in pain control and reducing acute inflammation.[19]

It is difficult to reconcile the negative findings of our study with published reports of reduced pain, increased pain threshold, or improved functional scores in NP patients in response to treatment with the InterX or a similar device—the ENAR (Electro Neuro Adaptive Regulator).[20-22] According to 1 report, after twelve 15-minute sessions with ENAR over a 6-week period, patients reported a significant reduction in the intensity of NP and improved NDI and Patient-Specific Functional Scale (PSFS) scores measured up to 24 weeks post-treatment.[22] In agreement with our findings, Schabrun et al[7] reported no changes in pain or NDI scores in their study of InterX effects on patients with chronic NP, although improvements in the Patient-Specific Functional Scale scores were observed 5 days after a single 10-minute application of InterX. In a different clinical model, Selfe et al[21] reported that after 17 treatments with NIN (InterX5000), over an 8-week period, there was clinically important but statistically insignificant reduction of pain in patients with knee osteoarthritis. Thus, differences between our data and those reported in the literature on pain control and improved functional scales in patients with NP in response to interactive neurostimulation may well be due to issues related to study design and protocol followed in the different studies.

Our laboratory observations were fully corroborated by the lack of clinical evidence of pain reduction or improvement of functional activity in the studied patients. However, it is feasible that NIN may be clinically effective in reducing the inflammatory response in different clinical models involving acute inflammation, such as had been reported for postoperative trauma.[4-6] Such an effect may be consistent with the postoperative effects of TENS. For example, TENS has been shown to alleviate post-thoracotomy pain and lower the serum levels of TNFα, IL-6, and IL-10 in patients who underwent surgery for resectable lung cancer.[23] The biological mechanism of electrotherapy-related effect on the production of cytokines is not clear, although its effect on electrical activity of muscles has been postulated.[24] It is well established that within a week after major orthopaedic surgery, ex vivo production of certain cytokines including TNFα and IL-10 becomes compromised and is associated with a significant reduction in the number of inflammatory cells in the peripheral blood.[25] Thus, it is feasible that the anti-inflammatory potential of TENS or similar electrotherapy devices is adjunct to surgical trauma-associated down-regulation of cytokine synthesis.[26,27] In all studies reporting on clinical efficacy of InterX in surgical patients, the treatments were initiated within 24 hours after surgery,[4-6] which coincides with the time of physiologically

Table 2. *The Effect of InterX5000 Therapy on the Levels of Proinflammatory Cytokines, IL-1, and IL-6 in Patients With NP and Asymptomatic Controls* [a]

Cytokine						
		IL-1 (ng/mL)			IL-6 (ng/mL)	
Treatment	Baseline	Test 1	Test 2	Baseline	Test 1	Test 2
InterX	2.35 ± 0.3	2.22 ± 0.46	2.31 ± 0.2	11.4 ± 1.06	10.9 ± 0.8	10.7 ± 1.2
Placebo	2.4 ± 0.16	2.22 ± 0.26	2.03 ± 0.03	11.1 ± 1.3	10.1 ± 1.1	9.3 ± 0.7
Asymptomatic subjects	1.17 ± 0.12			7.5 ± 0.5		

IL, interleukin.

[a] The in vitro synthesis of IL-1 and IL-6 was determined in tissue culture supernatants from patients with NP investigated at the time of admission into the study (baseline) and subsequently after 3 (test 1) and 6 (test 2) applications of InterX5000 or placebo therapy. Levels of IL-1 and IL-6 productions in patients with NP were compared with those generated in blood cultures from asymptomatic subjects.

reduced capacity for generation of inflammatory response. As the effectiveness of InterX therapy was suggested to ensue from its ability to change skin impedance,[3] this type of treatment could increase blood flow into the treated region and, by altering the cellular composition of the wound area, promote its healing and reduce local edema. However, this scenario is clearly not applicable to NP patients investigated in the present study.

In conclusion, the present study offers no experimental evidence that the application of NIN through InterX5000 reduces the magnitude or duration of the inflammatory response in NP patients. Further basic and clinical studies are necessary to clarify the exact mode of action of this device before recommendation of its inclusion into the standard of care for NP patients.

Limitations

The study was limited to investigating the effects of InterX5000 on NP patients. The results might be different in patients with acute NP. Furthermore, the NP patient population enrolled in the study was heterogeneous with respect of etiology, precise pathophysiology, and the duration of the problem. Pain intensity and functional limitations varied among study participants, and this may be related to the small sample size. In addition, the physiological effects of InterX5000 application may differ from those obtained with other InterX models (eg, InterX1000 or 5002).

Future Studies

In view of the limitations above, future studies may include an acute NP patient population, and a more tightly selected patient population with respect to pain level and functional disability.

Conclusion

The present study offers no experimental evidence that the application of NIN through InterX5000 reduces the magnitude or duration of the inflammatory response in NP patients. Further studies on a larger sample of homogeneous NP patients may be necessary to determine the efficacy of this device before recommendation of its inclusion into the standard of care for such patients.

Practical Applications

- Levels of biomarkers of inflammation encompassing proinflammatory and anti-inflammatory mediators are elevated in patients with chronic mechanical NP.
- Application of InterX5000 does not alter/normalize the inflammatory profile or improve functional limitations in patients with chronic NP.
- The use of InterX5000 to treat patients with chronic mechanical NP requires further investigation.

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Funding Sources and Potential Conflicts of Interest

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Contributorship Information

Concept development (provided idea for the research): J.J.T., L.W., J.T-I., H.S.I.

Design (planned the methods to generate the results): J.J.T., L.W., J.T-I., H.S.I.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): J.J.T., J.T-I., H.S.I.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): J.T-I., J.J.T.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): J.T-I., M.McG.
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