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CLINICAL APPROACHES

Cytokine changes with microcurrent treatment of fibromyalgia associated with cervical spine trauma

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Summary *Objective*: Patients who have fibromyalgia syndrome (FMS) associated with cervical spine trauma have distinct pain descriptors and physical examination findings. Currently, there is no effective treatment for fibromyalgia. Microamperage current provides physiologic current flow and has been used in the treatment of some pain syndromes. In this uncontrolled retrospective analysis of patients receiving microcurrent treatment for fibromyalgia following cervical spine trauma, subjective pain scores are utilized as a primary outcomes measure. Accompanying changes in inflammatory cytokines are examined in a subgroup of the same patient population to test the hypothesis that microcurrent treatment produces substantial measurable objective and subjective outcomes supporting the efficacy of this treatment.

Methods: A total of 54 consecutive patients meeting the ACR diagnostic criteria for fibromyalgia were treated with microamperage current. Blood samples on a subset of six patients were analyzed using a recycling immunoaffinity chromatography system to identify objective changes accompanying subjective pain scores.

Results: Five patients did not tolerate treatment. The remaining 49 patients reported reduction in pain on a 10-point visual analog scale (VAS) from an average baseline score of 7.3 ± 1.2 to 1.3 ± 1.1 with the first treatment. ($P < 0.0001$). Thirty-one patients reported symptomatic relief from fibromyalgia following an average of eight treatments. Median time to improvement was 2 months and the actuarial recovery curve reached 100% at 4.5 months. Interleukin-1, Interleukin-6 and substance P levels were all reduced from 330 to 80 pg/ml ($P = 0.004$), from 239 to 76 pg/ml ($P = 0.0008$), and from 180 to 54 pg/ml ($P = 0.0001$), respectively, in the first 90-min treatment. Tumor necrosis factor (TNF)-α was also reduced from 305 to 78 pg/ml ($P = 0.002$). During the same time period, beta-endorphin and cortisol both increased from an average of 8.2 to 71.1 pg/ml ($P = 0.003$), and 14.7 to 105.3 μg/ml ($P = 0.03$), respectively.

Conclusion: In a retrospective study based on analysis of subjective VAS pain scores for 54 patients, symptoms of fibromyalgia following cervical spine trauma were successfully

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treated with microamperage current. In a subgroup of the same patients, subjective pain improvement scores were accompanied by substantial reduction in serum levels of the inflammatory cytokines IL-1, IL-6, and TNF-α, and the neuropeptide substance P. Beta-endorphin release and increases in serum cortisol were also observed in these patients during the same treatment period. The subjective outcomes scores in conjunction with biological markers for pain and pro-inflammatory cytokines observed in response to this treatment protocol are important preliminary findings. Based on the observations reported in this analysis, controlled prospective clinical studies to evaluate the clinical efficacy of microcurrent treatment of FMS associated with cervical spine trauma are warranted.

Introduction

Fibromyalgia syndrome (FMS) is a potentially disabling chronic pain condition, and is the most frequent cause of chronic widespread pain (Kransler et al., 2002). It is 13 times more common following cervical spine injury compared to its association with leg fractures, and there is an overall 22–24% prevalence following cervical spine injuries, amounting to approximately 1.5 million patients whose fibromyalgia may be associated with cervical spine trauma (Buskila et al., 1997; Wolfe, 1990).

In our experience, patients with cervical trauma-associated fibromyalgia describe full body pain and pain in the hands and feet and use descriptors such as "burning", "stabbing", "sharp", and "shooting", compared with terms such as "dull" and "diffuse aching" used by other fibromyalgia patients. In general, there is a higher incidence and greater severity of headaches in this group and a characteristic affective quality to the pain that is reminiscent of central pain. Clinically, this is qualitatively different from the headache complaints and affective quality that accompany fibromyalgia not associated with cervical trauma. In our experience, patients with cervical trauma onset fibromyalgia have hyperactive patellar reflexes and specific dermatomal hyperesthesia indicating a degree of spinal cord and nerve root irritation not seen in fibromyalgia that is unrelated to cervical trauma. Despite these clinical observations, however, an unequivocal causal link between fibromyalgia and cervical trauma has not been established.

Currently, there is no widely accepted effective treatment for fibromyalgia, and symptoms persist for years even with various approaches to therapy (Sprott, 2003). Patients are usually managed with opiate or anti-inflammatory medications and antidepressants and a variety of other medications for associated conditions and symptoms. To date, the efficacy of non-pharmacological interventions for FMS remains unclear, and suggests a need for more rigorous analytical methods and objective outcome measures (Sim and Adams, 2002).

Pro-inflammatory cytokines such as Interleukin-1 (IL-1) and IL-6 can be useful markers in the study of chronic pain because they are known to enhance nociception by changing ion channels regulated through second messenger cascades (Satoh, 2000). Interleukins are known to contribute to cyclooxygenase-2 (COX-2)-mediated release of prostaglandins resulting in increased voltage-dependent calcium inflow in nociceptive fibers (Vanegas and Schaible, 2001). Substances of vascular origin including IL-1, IL-6, and the cytokine inducer, tumor necrosis factor alpha (TNF-α), act as hyperalgesic factors. Activity and metabolism of sensory fibers are mediated by interaction with inflammatory infiltrate produced by immune cells in response to tissue injury (Rittner et al., 2002). The properties of nociceptors and the ability to transmit pain have been aggressively targeted in the development of analgesics, however, non-pharmacological approaches for pain relief by cytokine modulation has been less frequently reported.

Other useful biological markers associated with pain include cortisol, beta (β)-endorphins and substance P (Tennant and Hermann, 2002). The hypothalamic–pituitary–adrenocortical (HPA) system releases cortisol from the adrenal cortex in response to stimuli, and therefore, plasma cortisol is a physiological marker of HPA activity, most notably in response to stress. The analgesic properties accompanied or mediated by β-endorphin release has been reviewed extensively in the literature, as have the effects of substance P related to pain transmission and modulation of nociception in the spinal cord (Furst, 1999).

Microamperage current (microcurrent) provides electrons at physiologic amperage in millionths of an ampere, or 10^{-6} amperes (amps) and has been used for the treatment of myofascial pain syndromes (McMakin,1998, 2004). Microcurrent treatment has also been used to increase the rate of

healing in non-union fractures (Abeed et al., 1998; Kahn, 1982) and sports injuries. The mechanism of action is unknown and is likely related to mechanisms that regulate intracellular Ca^{2+} homeostasis (Lambert et al., 2002). A recent randomized, controlled clinical study using non-invasive electrical stimulation, reports an association with β-endorphin release in the treatment of chronic back pain (Gabis et al., 2003).

In this study, we hypothesize that cord function is normalized in a group of FMS patients by passing polarized two-channel square wave microamperage current along the cord from neck to feet at 40 and 10 Hz. The study seeks to evaluate the efficacy of microcurrent treatment by examining trends in patient-reported pain scores pre- and post-treatment and accompanying changes in inflammatory cytokine and pain-associated neuropeptide levels in a representative subset of patients.

Methods

Patients

Fifty-four consecutive patients who met the ACR diagnostic criteria for fibromyalgia, having 11 out of 18 tender points responsive to less than 4 kg/in^2 and non-restorative sleep lasting five or more days, with cervical trauma-associated onset presented to our private clinic for treatment during an 18-month period. All patients completed a visual analog scale (VAS), for reporting subjective assessment of pain on a scale of "one" to "ten". Cytokine and peptide measurements to identify physiologic markers accompanying the changes in subjective pain were conducted in a small subset of patients. Six subjects were randomly selected for analysis of Interleukins 1 and 6, TNF-α alpha, cortisol, substance P, and β endorphin. The subset group did not differ significantly in either age ($P = 0.43$, t-test) or pain chronicity ($P = 0.25$ t-test) from other subjects. One patient with regional myofascial pain syndrome associated with cervical trauma who did not meet the ACR criteria for fibromyalgia served as a control for the subset group. Myofascial pain syndrome was evaluated by palpation of taut bands and the presence of active myofascial trigger points causing referred pain.

Microcurrent treatments

The selected frequencies of 40 and 10 Hz were determined by trial and error over a period of approximately 1 year during which different frequency combinations were evaluated. Immediate reduction in pain was observed in cervical spine trauma fibromyalgia patients treated with this frequency combination (data not shown). Pain that was not associated with cervical trauma was not affected by these frequencies. No other frequency combination was found to be effective in reducing the pain from cervical spine trauma fibromyalgia. Figure 1 shows the patient set up for in-office treatment. It was noted that the current had to be applied in such a way that the conducting medium wrapped from the posterior spine to the approximate location of the neural foramen on both sides of the neck. The conducting medium was applied in a warm wet towel wrapped around the neck and feet. No other method of applying current produced the observed effect.

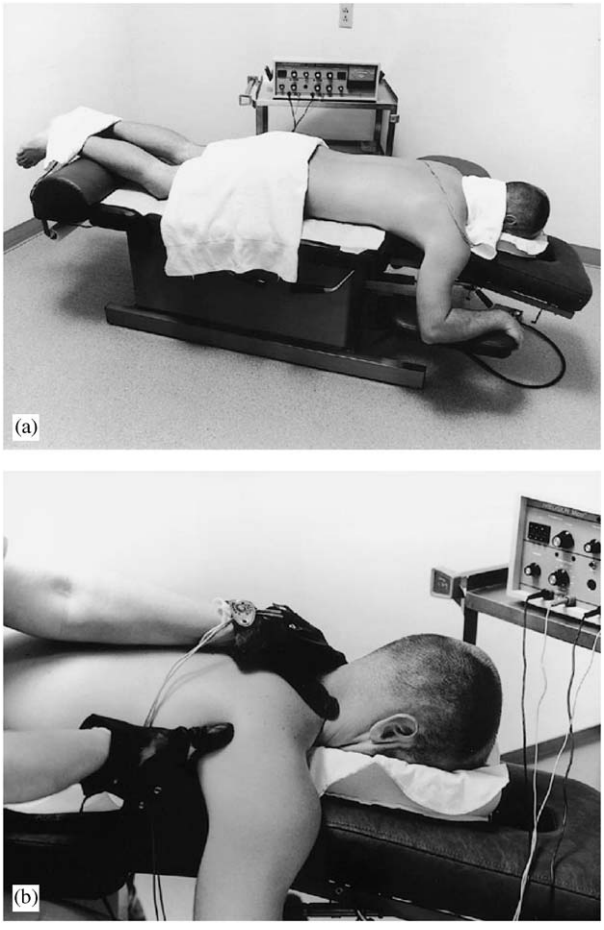

Figure 1 (a). Photograph of microcurrent treatment of low back. The patient may be treated prone or supine. The graphite glove with the positive leads is wrapped in a warm wet towel around the neck. The glove with negative leads is wrapped around the feet. The patient is covered with a blanket to retain body heat during treatment. (b). Prone cervical myofascial paraspinal treatment. (With permission. Chaitow et al., 2003)

When treatment in the clinic was effective in reducing pain, the patient was fitted with a pocket-sized, battery-operated unit capable of providing polarized current and the desired frequencies on two different channels. The patients used 2×3 inch conductive pads placed over the spinous processes and wrapping the neck laterally to the approximate location of the exiting nerve roots and pads placed on the soles of the feet to complete the circuit. The patients were instructed to use the home unit to keep pain below a "three" (3/10) on the VAS.

Blood sample methodology

Blood was collected using finger lancets during a 90-min microcurrent treatment. Three to five samples were taken during a treatment session, most commonly during the first session. The sample was allowed to drop onto a clean sheet of chromatographic filter paper. The spots were air dried overnight, placed in sealed plastic bags and mailed to an independent testing facility. A 5 mm diameter circle was obtained from each spot, eluted and normalized for total protein content. Each eluate was analyzed by recycling immunoaffinity chromatography (Phillips and Krum, 1998), employing individual columns containing immobilized antibodies against human IL-1 and IL-6, TNF-α, substance P, β-endorphin and cortisol. Released analytes were detected by laser-induced fluorescence. Analytes of interest were measured by the fluorescence detector and compared to standard curves constructed by subjecting known standards to an identical extraction procedure.

Statistical methods

The Wilcoxon matched pairs signed rank sum test was used to compare pre and post treatment pain scores. The Mann–Whitney *U* test was used to test for differences in the change in pre- and post-treatment pain scores between different groups, for example, between those who discontinued treatment and those who remained in treatment.

Pearson's correlation coefficients and associated *P*-values were calculated to demonstrate whether sequences of biochemical values during a single treatment session were significantly correlated, for example, exhibiting a trend. The *t*-test was used to compare biochemical values at the start and end of the first treatment. Values of $P < 0.05$ were interpreted to signify correlations beyond what would be likely to occur by chance.

The changes in biochemical values were approximately linear, and therefore stepwise linear regressions were used to compare these changes between patients and the control, with an indicator variable coded as 0 for patients and 1 for the control being included. A second variable giving the treatment session number was also included in the linear regressions to check for differences in rate of change of the biochemical variable from session to session. The intervals between samples were approximately uniform, and since the precise timings were not always available, the intervals were assumed to be identical.

Results

The patient population had a mean age of 44 years (range 10–75). The cervical injuries were predominantly from motor vehicle accidents ($n = 36$), with a miscellaneous group of other accidents such as falls ($n = 4$) and lifting accidents ($n = 5$). Two injuries occurred following surgery presumably due to hyperextension of the neck during intubation for anaesthesia. Average chronicity in the group was 9.5 years with a range of 1–50 years. Five patients did not tolerate treatment, and were discontinued from the treatment protocol.

The average pain score before treatment was $7.3 \pm 1.2/10$ (range 5–10/10), compared to an average of $1.3 \pm 1.1/10$ (range 0–4/10) following the first treatment session ($P < 0.0001$). The treatment produced almost immediate relief of subjective pain in every patient treated beginning with the feet and moving cephalad until only the arm and hand pain remained. The time required to reduce the pain from incoming average of 7.3 to the ending average of 1.3 was approximately 90 min on the first treatment and approximately 40 min on subsequent treatments. In general, the time required to eliminate the pain became shorter at each subsequent treatment session.

All patients experienced pain relief with microcurrent treatment. The control patient did not show initial elevated levels of cytokines. The control patient's pain and cytokine profiles were unaffected by the 40 Hz, 10 Hz protocol, and her pain and trigger points were reduced with microcurrent treatment and frequency protocols useful for myofascial pain (McMakin, 1998). Fifty-eight percent (31/53) of the study subjects experienced resolution of fibromyalgia symptoms including improved tender point sensitivity and sleep quality following a period of ongoing office treatment and home care, with one patient

reporting relapse. Thirteen patients discontinued treatment for reasons not directly related to treatment. The discontinued patients averaged 3.5 treatments (range 1–9); improving patients averaged 4.4 treatments (range 3-7) and the recovered patients 8 treatments (range 2–17). Seven of the 13 patients (54%) who discontinued treatment did so within a week, precluding any chance of full recovery, and the others were treated for 3, 5, 7, 10, 13, and 17 weeks, respectively, limiting their chances of a full recovery. The patients who discontinued treatment experienced an 83% reduction in pain from an average of 7.5 to 1.3 by the end of the first treatment. ($P<0.0001$, Wilcoxon), which was not significantly different from the group that recovered. ($P = 0.55$ Mann–Whitney test), with an almost identical drop in pain in the two groups.

Changes in IL-1, IL-6, TNF-α and VAS pain scores during and between treatments are shown in Fig. 2. Stepwise linear regression demonstrates a significant difference between patients and the control ($P<0.001$) for IL-1, IL-6 and TNF-α and similar changes during the first treatment session were significant for all variables. The reductions in IL-1 were highly significant when considered both in total (step-wise linear regression P-value on time points <0.0001), and for individual patients at individual treatment sessions ($P<0.05$ for correlation coefficients for all sequences of IL-1 measurements). IL-1 was reduced from an average of 330 ± 39 to 80 ± 31 pg/ml ($P = 0.004$ t-test). IL-6 was reduced from an average of 239 ± 23 to 76 ± 38 pg/ml ($P = 0.0008$, t-test). TNF-α was reduced from an average of 305 ± 36 to 78 ± 35 pg/ml ($P = 0.002$, t-test). The pain VAS for the five responding patients was reduced from an average of 6.8 ± 0.58 out of 10 to 0 during the 90 min treatment ($P = 0.0003$, t-test). Correlations between VAS pain scale and all the variables were statistically significant with correlation coefficients ranging from 0.73 to 0.91.

Changes in substance P, cortisol, and β-endorphins during and between treatments are shown in Fig. 3. Substance P was reduced from 180 ± 31 to 54 ± 28 pg/ml ($P = 0.0001$, t-test), β-endorphins increased from an average of 8.2 ± 2.5 to 71.1 pg/ml±9.3 ($P = 0.003$, t-test), and cortisol increased

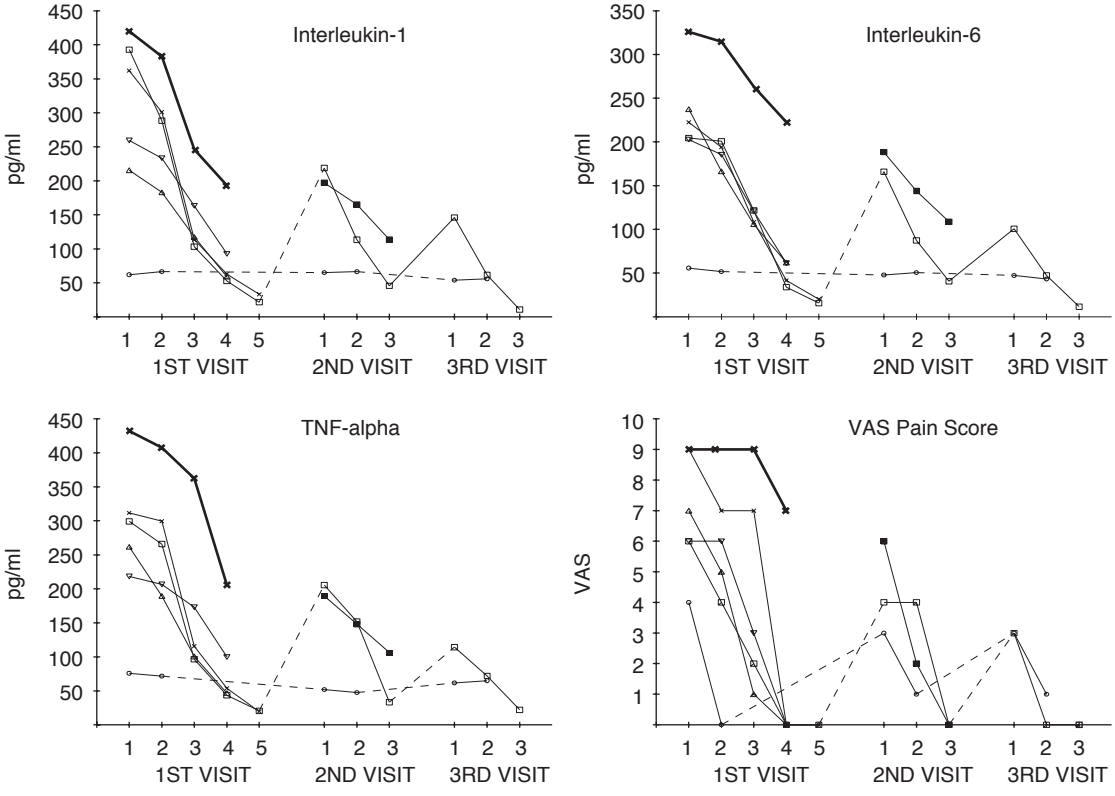

Figure 2 Changes in IL-1, IL-6, TNF-α and VAS pain scores during and between treatments. Key: each patient is represented by the same symbol for all variables. Broken lines indicate changes between the end of one treatment and the start of the next. Solid lines indicate changes during a single 90-min treatment in responding patients. The solid squares represent one patient who was sampled only on the second visit. The control patient is represented by the small open circles and shows no changes in cytokines, but did show changes in pain following non-protocol microcurrent treatment for myofascial pain. The heavy solid line indicates changes in one patient who did not tolerate treatment.

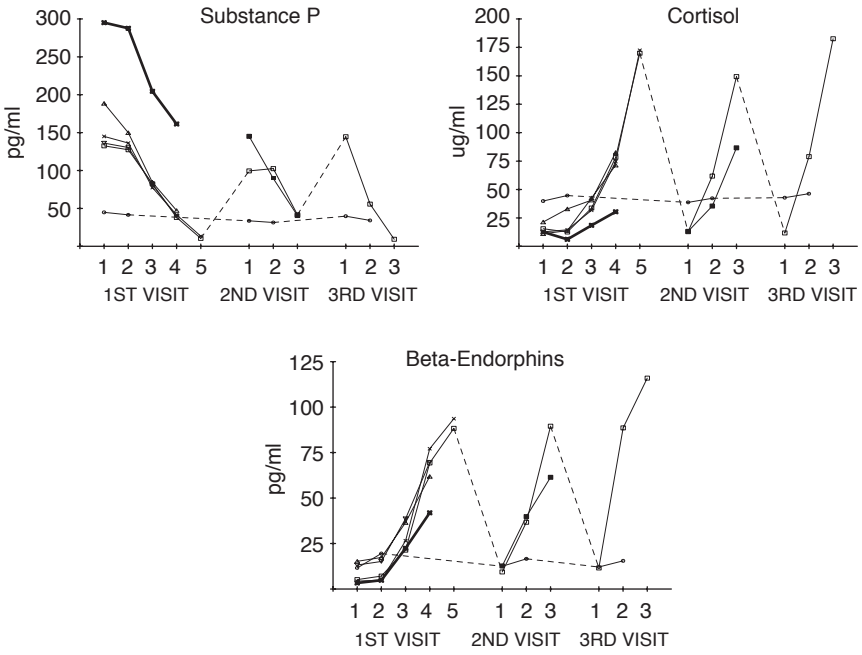

Figure 3 Changes in substance P, cortisol, β-endorphins during and between treatments. Key: each patient is represented by the same symbol for all variables. Broken lines indicate changes between the end of one treatment and the start of the next Solid lines indicate changes during a single 90-min treatment in responding patients. The solid squares represent one patient who was sampled only on the second visit. The control patient is represented by the small open circles and shows very little change. The heavy solid line indicates changes in one patient who did not tolerate treatment.

from 14.7 ± 1.8 to $105.3 \pm 28.2\,\mu g/ml$ ($P = 0.03$, t-test) during the first 90-min treatment.

Discussion

The causal link between FMS and cervical spine trauma may be attributable to commonly occurring posterolateral or central annular tears, and tears between the disc and endplate in these injuries, exposing the cord to the nucleus pulposus (Taylor and Twomey, 1993). The resulting inflammatory response from exposure, specifically to phospholipase A_2 (PLA_2), has been demonstrated to reduce nerve conduction velocity and produce nerve fiber degeneration, even in the absence of evidence of mechanical compression of the nerve root (Olmarker et al., 1993, 1995). The damaging effects of PLA_2 are dependent on concentration. (Ozaktay et al., 1995, 1998) The anterolateral pain tracts are immediately adjacent to the areas of the annulus most commonly damaged by trauma and would be exposed to the highest concentrations of PLA_2. Patients with fibromyalgia associated with cervical trauma used pain descriptors and created pain diagrams reminiscent of central pain and have physical examination findings indicating spinal cord and nerve root irritation. According to Kandel and Schwartz (1985): ''Central pain can arise not only from pathologic lesions in the thalamus but also from (neurosurgical) lesions placed anywhere along the nociceptive pathway from the spinal cord and brain stem to the thalamus and cortex.'' The authors hypothesize that the causal link between cervical trauma fibromyalgia and cervical injuries may be related to changes in conductivity in the anterolateral pathways created by exposure to high concentrations of PLA_2 from an immediately adjacent injured disc. It is not known if or how the application of microamperage current and the frequencies 40 and 10 Hz along the spinal cord would improve or normalize conductivity.

While information regarding cellular responses to intervertebral disc damage is just recently emerging, differences in cell morphology have been demonstrated to occur between cells of the nucleus pulposus and annulus fibrosis in response to micromechanical loading (Setton and Chen, 2004). The factors that control micromechanical stimuli and their effect on the regulation of cytokines and the mediators of pain and inflammation remain critically understudied. Among the subjects participating in this study for whom MRI images were available, all but one demonstrated disc

bulging or a contained herniation usually at the C5–C6 or C4–C5 level, as determined by a consulting radiologist. Plain film radiographs showed anterolisthesis or retrolisthesis above or below the disc bulge in three cases. Flexion/extension films showed segmental hypermobility or increased translation at or above the level of disc injury. Imaging studies were not available for all participants, however these findings are supportive of a cervical spine trauma/FMS link and warrant further investigation.

Most cytokines, while primarily appreciated as mediators of the immune system, are also produced by the peripheral and central nervous system and have been shown to induce or increase neuropathic pain (Elenkov et al., 2000; Sommer, 2001). While the immune pathophysiology of FMS remains unclear, there is suggestive evidence from experimental models of FMS in that treatment based on pharmacological manipulation of the sympathetic–immune interface shows promise (Van West and Maes, 2001).

Taken together, the observed reductions in inflammatory cytokines, the increase in β-endorphin release and the accompanying subjective data reporting pain relief can be explained by a moderate anti-inflammatory effect in this patient group that is modulated by the microcurrent treatment. These biological markers have all been identified as primary afferent transmitters involved in human responses to nociceptive input (Furst, 1999). The increase in cortisol plasma levels is consistent with endorphin release via the ACTH precursor pathway. Furthermore, the cortisol elevation is unlikely to be associated with a stress response since decreasing neuropeptide Y levels were observed in these patients during the same time period (data not shown). However, it cannot be ruled out that the symptomology of FMS is often complicated by alterations in nearly all of the hormonal feedback mechanisms that have been observed clinically, including those specifically involving cortisol release (Neeck, 2000; Reidel et al., 2002).

In the group of patients participating in the biological marker arm of the study, one patient out of six who continued treatment experienced a full recovery from fibromyalgia with no relapse after 18 months. Full recovery was defined as no longer meeting the ACR diagnostic criteria for fibromyalgia in regards to pain, fatigue, tender point count and sleep quality. The patients who discontinued treatment reported recurrence of their pain during subsequent visits. These observations strongly support further investigation into use of this method as an effective treatment for fibromyalgia associated with cervical spine trauma.

In our experience, no other treatment procedures or frequency combinations are effective in pain reduction or the treatment of this type of fibromyalgia. And it should be noted that we have not observed efficacy of this treatment for reducing any other type of pain including fibromyalgia not associated with cervical trauma. Conclusions supported by a placebo control group and comprehensive analysis of biological and imaging studies in all study participants is beyond the scope of this study in this particular group of subjects whose outcomes data were collected and analyzed retrospectively. Nonetheless, the findings associated with this treatment in an otherwise challenging group of patients suggests that this treatment modality warrants further characterization in studies that include sham treatments, matched controls and expanded monitoring for cytokines and neuropeptides.

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