Inhibitory effects of biofeedback electrostimulation therapy on pain and cortisol levels in chronic neuropathic pain: A randomized-controlled trial

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ABSTRACT

Objectives: This study aims to investigate the effectiveness of biofeedback electrostimulation therapy (BEST) in chronic neuropathic pain and to evaluate changes in perceived level of pain and level of blood cortisol before and after treatment.

Patients and methods: This single-blind, prospective, randomized-controlled study included a total of 20 patients (8 males, 12 females; mean age: 53.5±13.8; range, 31 to 82 years) with chronic neuropathic pain between January 2014 and June 2014. The patients were randomized to BEST (n=10) or placebo (n=10) group. Pain was measured using the Visual Analog Scale, and serum cortisol levels were measured before and after treatment.

Results: There was no significant difference in the baseline demographics, diagnosis, and treatment modalities between the groups. Approximately 50% patients in the treatment group reported that the treatment was effective, compared to 30% in the placebo group. Pain score reduction after treatment in the BEST group was significant ($p<0.05$), while it was not significant in the placebo group ($p=0.4$). Cortisol levels significantly reduced only in the BEST group after treatment ($p=0.013$).

Conclusion: The BEST yields reduction in pain severity and cortisol levels. Based on these results, it seems to be effective in the treatment of chronic neuropathic pain after a single treatment and may be more effective for long-term management.

Keywords: Biofeedback electrostimulation therapy, cortisol, neuropathic, pain.

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[1] Neuropathic pain (NP) has been defined by IASP as pain initiated or caused by a primary lesion or dysfunction in the nervous system.[2]

The underlying causes of these disorders include infections, trauma, metabolic abnormalities, chemotherapy, surgery, irradiation, neurotoxins, inherited neurodegeneration, nerve compression, inflammation, and tumor infiltration.[1,3] The diagnosis of NP is based on a medical history, review of systems, physical and neurological examination, and appropriate laboratory studies including blood and serologic tests, magnetic resonance imaging, and electrophysiological studies.[3,4]

The drugs used to treat NP can be broadly divided into two categories: medications used to treat other conditions, but found to be useful in reducing pain from nervous system damage, and analgesics. Combinations of medications appear to provide greater pain relief compared with monotherapy, although there is not a great deal of evidence surrounding combination therapy. Non-pharmacological approaches to the treatment of NP also exist; these include physical medicine, and behavioral, interventional, surgical, and neuromodulation approaches. The mechanisms for

NP and its treatment differ from those for nociceptive pain.[3,5]

Biofeedback electrostimulation therapy (BEST) is implemented using a peripheral electrostimulation device. It is United States Food and Drug Administration (FDA)-approved for symptomatic relief and management of chronic, intractable pain and as an adjunctive treatment in the management of post-surgical and post-traumatic pain. The BEST generates electrical impulses (sine waves) that are physiologically similar to neurological impulses observed in the "C" nerve fibers and "A" fibers.[4] The electrical signal characteristics of BEST are short-duration pulses of high voltage amplitude and very low duty cycle, average currents in the microcurrent range, and dampened bi-phasic sinusoidal waveforms. The advantages of the BEST device include fast relief from acute and chronic pain, pain relief of up to 12 h, and asymmetrical wave signals and biofeedback which minimize habituation and accommodation effects on the body.[5] The device seeks decreased impedance on the skin by sticking to acupuncture or electron deficient points, while gliding over the skin. These areas may comprise of injured or diseased tissue or may be associated with an organ or corresponding structure within that anatomical segment. The device, then, communicates via electrical impulses with the neuroendocrine system through direct contact with the skin, sending signals through the epidermis and dermis to the "A" and "C" fibers.

Pain produces stress and stress worsens pain by affecting mood, sleep, and pain threshold. Some hormones respond to stress, such as cortisol. Elevated cortisol levels are found in many diseases, including infectious, aging-related, depression, and depression-associated conditions. It has been suggested that high cortisol levels play a major causative role in these diseases, implying that anti-cortisol drugs may represent beneficial new therapies. In the present study, we aimed to investigate the effectiveness of BEST in chronic neuropathic pain and to evaluate changes in perceived level of pain and level of blood cortisol before and after treatment.

PATIENTS AND METHODS

This single-blind, prospective, randomized-controlled study was conducted in the pain clinic of University Malaya Hospital, Malaysia between January 1st, 2014 and June 30th, 2014. A total of 20 patients (8 males, 12 females; mean age: 53.5±13.8; range, 31 to 82 years) with CNP were included in this study. Inclusion criteria were as follows: having CNP according to the ID pain scores); duration of symptoms of more than three months; symptoms including dysesthesias, paresthesia, allodynia, pins and needles, numbness, or burning sensations; and receiving regular medication to control pain. Exclusion criteria were as follows: age <18 years; being pregnant and/or lactating; having a functional cardiac pacemaker or cardiac defibrillator; intoxicated individuals; having severe mental disorders; organ transplant recipients; presence of malignancy; presence of pain of central origin or proven or suspected primary brain lesion, e.g., traumatic brain injury or stroke; undiagnosed pain syndromes; and presence of epilepsy. A written informed consent was obtained from each patient. The study protocol was approved by the Medical Centre Research Ethics Committee of University Malaya (No. 1009.9). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Randomization and intervention

Randomization was performed using block randomization to either the BEST group (T, n=10) or the placebo group (NT, n=10) using sealed envelopes (blocks of 10). The treatment group received treatment using the BEST device and the placebo group received treatment using a sham BEST device.

For the treatment group, the site of pain was determined and marked. The device, using the Y electrode, was placed on the skin outside the intended area of treatment. The initial mode was set at deep stimulation mode and the level of power was adjusted to the level that the patient felt comfortable with. Next, the electrode was moved steadily and firmly in one direction across the intended area of treatment (painting) to locate the active site.

Active sites are areas of the skin that are different from the surrounding skin. Features of active sites include: change of color (redder or paler), change of sound produced by the device (sudden increase or decrease in amplitude), stickiness or increase in resistance, sensitivity of the skin (more or less sensitive), and primary signs (small changes to the spot even before treatment begins; i.e., itching, redness, dryness, or texture difference). When the active site was found, the device was kept on the area for 1 to 2 min. This was to allow the device to establish biofeedback balance. Then, the Y-electrode was moved over the area and painted in four directions in a specific order (top to bottom, right to left, left to right, bottom to top) until the sliding sensation was smooth and similar to that of the surrounding skin. This was followed by placing two self-adhesive pads over the area for treatment

in repetitive strain injury mode for about 20 min. The recommended duration for treatment sessions is 30 min.[6] The patients randomized to the placebo arm were treated with a sham BEST device for 30 min in a similar fashion to the treatment group. However, no current was delivered through the Y electrode or the self-adhesive pads.

Outcomes and follow-up

Baseline data for the study were collected using a standardized form and included baseline demographic data (initials, age, sex, and race), diagnosis, and current medication. Baseline pain scores were obtained using the Visual Analog Scale (VAS) and 20 mL of blood was drawn to assess baseline cortisol levels. To ensure patients were well hydrated, they were required to drink water before and after treatment. After treatment, pain scores were recorded using the VAS and another 20 mL of blood was taken. Blood samples pre- and post-treatment were collected, serum was isolated, and cortisol levels were assayed by direct chemiluminescence (Advia Centaur XP, Siemens, Dublin, Ireland).

Statistical analysis

Power analysis and sample size calculation were performed using the GraphPad StatMate version 2.0 software (GraphPad Inc., CA, USA). The sample size was previously calculated based on mean and standard deviation values of a pilot study obtained from previous treatments. Accordingly, at least 10 participants were required for a test power of 80% with an alpha significance level of 0.05.

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (interquartile range [IQR]) or number and frequency. For analysis of

data normality, we used the Shapiro-Wilk test, followed by the Friedman test for non-parametric data. Baseline demographic data were analyzed using the Fisher's exact test and Mann-Whitney test. The Wilcoxon signed-rank test was used to compare between pain score and serum cortisol level. A *p* value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference in the baseline demographics, diagnosis, and treatment modalities between the groups (Table 1). Although not statistically significant, the number of male patients was higher in the BEST group compared to the placebo group (p=0.143).

The majority of the patients had back pain and there were no significant differences in terms of treatment modalities between the BEST group and the placebo group (Table 2).

Measures of patient satisfaction showed that 50% of patients in the BEST group reported that the treatment was good compared to only 30% in the placebo group. Only 20% of the treatment group and 30% of the placebo group reported that the treatment modalities were not effective at all. As a result, 80% of the patients in the BEST group and 70% of the placebo group were willing to undergo treatment again (Table 3).

Table 4 shows the pain scores and serum cortisol levels of the patients in the BEST group and placebo group before and after treatment. Pain scores fell from 7.5 to 3.5 (p≤0.05) in the BEST group, whereas the scores fell from 5 to 4.5 (p=0.4) in the placebo group. Changes in the serum cortisol level before and after treatment in both groups are shown in Table 4. The BEST group showed a significant reduction in serum cortisol (p≤0.013), while the change in cortisol level in the placebo group was not significant (p≤0.074).

TABLE 1 Baseline demographic characteristics of patients (n=20)					
	BEST group (T, n=10)		Placebo group (NT, n=10)		
	n	Mean±SD	n	Mean±SD	*p**
Age (year)		53.5±13.8		54.0±15.6	0.971
Sex					0.143
Male	6		2		
Female	4		8		
Race					1.0
Indian	6		5		
Non-Indian	4		5		

BEST-RSI: Biofeedback Electrostimulation Technology with RSI mode for chronic pain; SD: Standard deviation; * Mann-Whitney U test.

TABLE 2
Patient diagnosis and treatment modalities

	BEST group (T, n=10)	Placebo group (NT, n=10)	
	n	n	p
Diagnosis			0.7*
Back pain**	5	5	
Neck pain†	1	1	
Upper limb pain‡	1	1	
Lower limb pain¶	0	1	
CRPS	3	1	
Fibromyalgia	0	1	
Treatment			1*
Paracetamol			
Yes	3	3	
No	7	7	
NSAID			1*
Yes	5	3	
No	5	7	
Opioids			1*
Yes	6	7	
No	4	3	
Gabapentin/pregabalin			1*
Yes	6	6	
No	4	4	
Tricyclic antidepressants			0.582*
Yes	1	3	
No	9	7	
Topicals			1*
Yes	0	1	
No	10	9	

BEST-RSI: Biofeedback Electrostimulation Technology with RSI mode for chronic pain; CRPS: Complex regional pain syndrome; NSAID: Non-steroidal anti-inflammatory drug; * Fisher's exact test; ** Degenerative spine/disc disease, prolapsed intervertebral disc, spinal stenosis; † Cervical spondylosis, cervical myelopathy; ‡ Brachial plexus injury, post rotator cuff repair scar pain; ¶ Post total knee replacement scar pain.

TABLE 3
Global patient satisfaction

	BEST group (T, n=10)	Placebo group (NT, n=10)	
	n	n	p*
Global satisfaction			0.436*
Good	5	3	
Satisfactory	3	4	
Not effective	2	3	
Try again			1.0**
Yes	8	7	
No	2	3	

BEST-RSI: Biofeedback Electrostimulation Technology with RSI mode for chronic pain; * Mann-Whitney U test; ** Fisher's exact test.

TABLE 4
Effect of BEST on pain scores and serum cortisol

	BEST group (T, n=10)					Placebo group (NT, n=10)				
	Preoperative		Postoperative			Preoperative		Postoperative		
	Median	IQR	Median	IQR	p	Median	IQR	Median	IQR	p
Pain score	7.5	4.5	3.5	4.5	0.05	5	2.75	4.5	4.25	0.4
Cortisol	219	189.5	170	121.5	0.013	281	171.25	273	198	0.074

BEST: Biofeedback electrostimulation therapy; IQR: Interquartile range; p value was calculated using the Wilcoxon signed-rank test.

DISCUSSION

The BEST device provides non-pharmaceutical, non-invasive, and ongoing pain relief. It has been shown in surveys to reduce the need for pharmaceutical pain relievers and improve patients' ability to take part in daily activities.[4,5] It has been shown to lack ongoing or significant side effects. There are no existing data on the effectiveness of BEST in the treatment of CNP or the purported mechanism of action with regard to inducing or reducing the production of blood biomarkers. In this study, we assessed the efficacy of this device in treating patients with CNP and measured serum levels of cortisol before and after treatment. Our results showed a reduction in pain score, and a reduction in serum cortisol levels after treatment. Similar to pain relief with transcutaneous electrical nerve stimulation (TENS), BEST pain relief is mediated by high intensity and high frequency electrical pulses which stimulate the larger Aα and Aβ fibers that, in turn, activate the inhibitory interneurons in lamina II and reduce nociceptive input to the dorsal horn.[4] The excitatory neurotransmitters, glutamate, and substance P have been shown to be reduced in the spinal dorsal horn in animal model studies.[5,7] In addition, it has been proposed that TENS-like devices induce or reduce the release of biomarkers such as nitric oxide, cortisol, cytokines, endorphins, and neuropeptides, into the blood circulation.[8]

In the current study, a significant pain reduction was observed in the BEST group, compared to the placebo group. The slight decline in pain scores recorded for patients in the placebo group indicates that the act of rubbing the skin also reduces pain. Melzack and Wall[4] first proposed the gate control theory in 1965, which explains the likely mechanism of the effect in the placebo group. The non-painful input closes the gates to painful input by activation of non-nociceptive Aβ fibers that inhibit firing of the nociceptive fibers in the laminae at the dorsal horn of the spinal cord.[6] Thus, the act of rubbing the skin with the probe prevents pain sensations from travelling to the central nervous system. However, the reduction of the pain score in the placebo group was too small to be considered statistically or clinically significant. The majority of patients who were treated with the BEST device rated the treatment as good. This further confirms that BEST is truly effective in reducing pain. The efficacy of the BEST device in treating CNP would prove beneficial to these patients, who usually have multiple medical problems, and are on multiple medications. The nature

and intensity of pain is usually poorly controlled. The BEST device can be utilized as an adjunct for the management of CNP. The device reduces impedance of the skin by prior movement of the electrode over the skin and therefore improves the penetration of the current into the deeper layers of tissue.[9] In addition, the treatment duration is longer per session as a result of the treatment protocol of reducing the skin impedance prior to application of the treatment pads. This would lead to a time-dependent increase in the concentration of endorphins and encephalin in the blood circulation and cerebrospinal fluid[10,11] and, thereby, resulting in improved pain relief. Finally, the device delivers a constantly changing waveform depending on the feedback it receives from the treatment area. This reduces the habituation and tolerance that is seen with long term TENS use. In a previous meta-analysis, BEST was applied for the treatment of urinary incontinence, bladder excessive activity, and symptoms of low urinary tract.[12] It was shown as a safe and effective method for the prevention and treatment of female stress urinary incontinence. Other studies showed that BEST prevented pain and diabetic ulcers by increasing the foot blood circulation in diabetes patients, and treatment of muscle damage with BEST reduced the severity of the symptoms.[12-18] Chronic pain disrupts one's life, lessens his/her ability to handle stress, weakens the immune system, and may result in anxiety, anger, and depression. Depression is one of the most common problems experienced by individuals with chronic pain.[14,16,17] Previous studies have confirmed that stress contributes to the development and exacerbation of chronic pain.[1] It also influences the sensitivity of peripheral nociceptors as a result of sympathetic activation and release of adrenal hormones.[13-16] In the current study, a significant reduction in serum cortisol levels was observed after a single session of BEST. The hypothalamic-pituitary-adrenal axis is stimulated by any inflammatory, emotional, or physical stress.[3] There is no greater stress than pain, and chronic pain may be accompanied by neuroinflammation.[4]

In our study, serum cortisol levels also reduced in the placebo group, although not statistically significantly. A form of massage may have produced some degree of relaxation. Previous studies have reported the stress-alleviating effects (decreased cortisol) of massage therapy in a variety of medical conditions and stress experiences.[17] Previous studies have also shown that massage therapy can lower cortisol levels, increase dopamine and serotonin, and lower excitatory hormones such as norepinephrine

and epinephrine.[13] Elevated levels of cortisol have been associated with elevated levels of stress, and it has been suggested that cortisol release causes stress, as described earlier.[12,14,16] A high cortisol level for prolonged periods can increase the risk of infection, high blood pressure, peptic ulcers, diabetes mellitus, osteoporosis, and depression.[11,12,18] It has been suggested that the reduction of serum cortisol by BEST plays a critical role in modulating stress and contributing to the reduction of CNP. Therefore, reducing stress in patients with NP is one of the main goals of pain treatment.

Nonetheless, there are some limitations to this study. It has a small sample size and the study power of this study was inadequate to provide good evidence of the efficacy of the BEST device. Future studies with a larger sample size are required. In addition, the treatment was only carried out once in patients who suffered from pain for long periods. The efficacy of this novel technology on a long-term basis needs to be evaluated, as studies have shown that TENS treatment efficacy spans a duration of 10 days to 6 weeks.[11] Also, the lack of follow-up to access whether the improvements achieved with the different parameters of electrical stimulation would last in the long-term.[18] As such, further studies involving more patients with repeated treatments in the longer term are required to further define the role of BEST in the treatment of CNP.

In conclusion, the BEST device is effective at producing pain relief and reducing serum cortisol levels in CNP patients after a single treatment session. It seems that BEST alters pain signals between the periphery and pain centers. Our results suggest that BEST causes relaxation in the pain area and reduces stress via the reduction of cortisol. These findings would likely benefit this group of patients, who are likely to have multiple medical problems and receive multiple medications. As an adjunct in the management of chronic pain, BEST would potentially help to reduce the dose and frequency of pharmacotherapy and, thus, reduce the side effects of these drugs. However, further studies are needed to establish the long-term efficacy of this treatment modality.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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