AVAZZIA BIOFEEDBACK ELECTROSTIMULATION THERAPY (AVAZZIA BEST): ITS EFFECT ON CHANGES IN PAIN BIOMARKERS ON CHRONIC NEUROPATHIC PAIN: A PROSPECTIVE RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Background

Avazzia Biofeedback Electrostimulation Therapy (BEST), a new and better improvised device as compared to conventional transcutaneous electrical nerve stimulation (TENS) is the latest generation of peripheral electrostimulation device. It is FDA approved for symptomatic relief and management of chronic, intractable pain and adjunctive treatment in the management of post surgical and post traumatic pain. It generates shorter duration electrical pulses of high voltage amplitude, and in very low duty cycle that are physiologically similar to neurological impulses observed in the "C" and "A" nerve fibers, hence offering promising pain control. To date, there are no studies evaluating the effectiveness of this novel device on chronic neuropathic pain patients. Thus, we aim to determine the efficacy of Avazzia BEST with changes in pain biomarkers level in this group of patients. In the study, perceived pain level before and after treatment were recorded, but only serum cortisol, β-endorphin and TNF-α level will be discussed in detail.

Method

This prospective randomized controlled study was conducted on 20 patients in University Malaya Medical Center between 1st January to 30th June 2014. Measured outcomes include changes in perceived pain level, and pre- and post-treatment level of pain biomarkers (cortisol, β-endorphin, and TNF-α). Data collected were analyzed using SPSS with the level of significance set at $p< 0.05$.

Result

Pain severity in both Avazzia BEST and Placebo showed statistically significant reduction as indicated by the P value of 0.005 and 0.039. All three pain biomarkers, serum cortisol, β-endorphin and TNF-α level observed a drop post treatment. Serum cortisol before (219.5) was significantly higher than after treatment with Avazzia BEST (170; p value 0.013). The drop in serum TNF-A level was however not significant statistically (p value 0.386). No correlation is observed between serum β-endorphin levels in Avazzia BEST.

Conclusion

Avazzia BEST technology demonstrated a marked improvement in perceived pain level based on numerical rating scale with a significant reduction in serum cortisol level after single dose treatment. A drop in serum TNF-α level was also observed, though not statistically significant. There is no correlation between the serum β-endorphin level and Avazzia BEST in this study. The long term efficacy of this device in correlation with changes in pain biomarkers is therefore yet to be elucidated.

ABBREVIATIONS

IASP	International Association for the Study of Pain
BEST	Biofeedback Electrostimulation Therapy
TENS	Transcutaneous Electrical Nerve Stimulation
SD	Standard Deviation
US FDA	United States Food and Drug Administration
TNF α	Tumour Necrosis Factor Alpha
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
P38 MAPK	p38 Mitogen-activated Protein Kinase
CES	Cranial Electrotherapy Stimulation
HPA	Hypothalamic-Pituitary-Adrenal axis
CRH	Corticotrophin Releasing Hormone
ACTH	Adrenocorticotrophic Hormone
ELISA kit	Enzyme-linked Immunosorbent Assay kit

TABLE OF CONTENT

		Page
1.	Introduction	1-3
2.	Methodology	4-8
	2.1 Sample Size	
	2.2 Randomization	
	2.3 Intervention	
	2.4 Statistical Analysis	
3.	Results	9-18
4.	Discussions	19-28
	4.1 Cortisol	
	4.2 Tumour Necrosis Factor-Alpha (TNF-α)	
	4.3 Beta Endorphin (β–Endorphin)	
	4.4 Limitations and Recommendations	
5.	Conclusion	29
6.	References	30-33

1. INTRODUCTION

Pain, as defined by the International Association for the Study of Pain (IASP), is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in term of such damage. Neuropathic pain is defined by the IASP as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system [1, 2]. Pain is an individual and subjective experience modulated by its psychological, physiological and environmental factors. The definition of pain underlies the complexity of its measurement and management. Many researchers have now examined a great number of chronic pain biomarkers to help quantify pain, but none have yet to be validated. Nonetheless, many studies report interesting findings correlating intensity of chronic pain with altered levels of biomarkers in blood which would be measured in this study.

Management of chronic neuropathic pain is multimodal and includes pharmacotherapy, physical therapy, occupational therapy, psychological therapy, interventional therapy and complementary therapy. Conventional TENS has been used widely in the management of acute and chronic pain of various causes, complimenting pharmacological treatment, aiming to improve analgesia and quality of life in chronic pain patients, however, its clinical effectiveness is still inconclusive.

With advancement in medical technology, a TENS-like, but newer medical electronic therapeutic and diagnostic device, is designed, emphasizing on the problem of chronic pain[3]. This device applies the use of subtle energy with the correct signature to influence physiologic mechanisms for tissue regeneration, pain abatement, and immune modulation in living organisms.

Avazzia BEST (Biofeedback Electro Stimulation Technology) device is the latest generation of peripheral electrostimulation device. It delivers higher frequency (1Hz to 500Hz), high intensity and short duration electrical pulses, producing direct effect on secretory C fibers and A fibers, and also significant CNS effect via C afferents to spinal ascending and opioid mediated descending inhibitory pathway. This induces release of nitric oxide, and neuropeptides into blood stream and initiate long term cascading effects and up-regulation of neuropeptides, endorphin, serotonin and enkephalin synthesis. This electrostimulation therapy begins with the application of a probe onto the treatment site. The probe transmits microcurrents and received signals from the treated area that reflects the changes in the physical properties of the affected tissue (biofeedback).

It is US FDA approved for symptomatic relief and management of chronic, intractable pain and adjunctive treatment in the management of post-surgical and post-traumatic pain. This BEST device produces analgesia that starts within moments and lasts up to 12 hours with both local and systemic pain relief. It also produces asymmetrical wave signals and biofeedback that minimizes habituation and accommodation effects of the body.

Till date, there is no study done to correlate the use of this device on changes in the perceived pain level to changes in pain biomarkers. Hence, this study is conducted with the aim to evaluate changes in perceived levels of pain and changes in pain biomarkers (cortisol, β−endophin and TNF α) on chronic neuropathic pain patients using Avazzia BEST device.

2. METHODOLOGY

This is a pilot study using Avazzia BEST device to deliver treatment to chronic neuropathic pain with regards to changes in pain biomarkers. It is a prospective randomized controlled single blinded trial conducted with the aim to correlate the efficacy of this device in providing analgesia and changes in pain biomarkers in circulation.

Inclusion criteria:

All patients with chronic neuropathic pain receiving treatment in Pain Clinic at University Malaya Medical Center:

1. Duration of symptoms: more than 3 months
2. Symptoms: dysthesias, parasthesias, allodynia, pins and needles, numbness, burning sensation
3. Patients are on regular medications to control pain.

Exclusion criteria:

Patients will be excluded from the study if any of the following criteria apply:

1. Age less than 18 years
2. Pregnant and/or lactating.
3. Patient with cardiac pacemakers or cardiac defibrillator
4. Intoxicated individuals
5. Patients with severe mental disorders
6. Patients with organ transplant
7. Patients with malignancy

8. Patients with pain of central origin or proven or suspected primary brain lesion eg. traumatic brain injury, stroke
9. Patients with undiagnosed pain syndromes
10. Patients with epilepsy

2.1 Sample size

Patients were recruited from the Pain Clinic of University Malaya Medical Centre, based on the pre-determined inclusion and exclusion criteria. A sample size of 20 patients is decided with 10 patients on each arm; treatment group and placebo group.

2.2 Randomization

The eligible patients were given information sheet explaining the electrostimulation therapy and noting its potential benefits. After obtaining consent, they were randomized into 2 groups by means of sealed envelopes:

1) Treatment group (A): receive microcurrents electrostimulation therapy using Avazzia BEST device.
2) Placebo group (B): receive treatment using a sham Avazzia BEST device.

2.3 Intervention

1. Patients were asked to come to the hospital at 8am on an agreed date for treatment.
2. Data for this study are collected using a standardized case report form. The following data was obtained on the day of recruitment:
    i. Demographic data (initials, age, gender, race)
    ii. Pain diagnosis

iii. Current medications and other complimenting treatment (eg. physiotherapy; occupational therapy)

iv. Pre-existing medical illnesses

v. Inclusion and Exclusion criteria checklist

3. Baseline pain score using the numerical rating scale is obtained and 20mls of blood is drawn for baseline biomarker levels.

4. To ensure patients are well hydrated, they are required to drink water before and after treatment.

5. Patients randomized to the treatment arm will receive treatment using the Avazzia BEST-RSI device.

5.1 The site of pain is determined and marked. Place the device using the Y electrode on the skin outside the intended area of treatment and adjust the level of power that the patients feel comfortable with. Then, the electrode is moved steadily and firmly in one direction across the intended area of treatment (painting) to locate the active site.

5.2 Active sites are area of the skin that is different from the surrounding skin.

Features of active site include:

- change of colour (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)
- primary signs (small changes to the spot even before treatment begins eg. itching, redness, dryness, texture difference, etc.)

5.3 When the active site is found, keep the device on the area of 1 to 2 minutes. This is to allow the device to establish biofeedback balance. Then, move the Y-electrode over the area and painting in 4 directions in the following order (top to bottom, right to left, left to right, bottom to top) until sliding sensation is smooth and similar compared to the surrounding skin.

5.4 Recommended time for treatment session is 30mins. Post treatment pain score is recorded from the patient. Post treatment blood sample will be taken at 30 minutes after the treatment.

6. For patients randomized to the placebo arm, the patients will be treated with a sham Avazzia BEST device for 30 minutes. Pain scores will be recorded and blood will be taken in the same manner as the patients in the treatment group.

7. Blood samples pre and post treatment will be analyzed using ELISA kits for levels of pain biomarkers – TNF-α, β-endorphin, and serum cortisol.

2.4 Statistical analysis

All data collected were analyzed using SPSS version 15.

Descriptive statistics is used to analyze data for demographics, pain severity and pain biomarkers (cortisol, β-endorphin and TNF-α) level to help describe and summarize all raw data in a meaningful way, allowing simpler interpretation. All values are expressed as measures of central tendency (mode, median and mean), and measures of spread (range, and standard deviation), unless otherwise stated. The grouped data is then summarized using a combination of tabulated description (i.e. tables), graphical description (i.e. graphs) and statistical commentary (i.e. a discussion of the results).

Student's unpaired T-test is used for analysis of the effects on pain biomarkers.
Mann-Whitney U test is also used to analyse the demographic data of both groups.
The level of statistic significant will be set at $p<0.05$.

3. RESULTS

A total of 20 patients were recruited for this pilot study with 10 patients on each arm, the Avazzia BEST group and the Placebo group.

Out of these 20 patients, ten (50%) had chronic low back pain, four (20%) had complex regional pain syndrome, two (10%) had chronic neck pain, two (10%) had upper limb pain, one (5%) had lower limb pain and the other one (5%) diagnosed with fibromyalgia (Table 2).

Patients had a mean age of 53.5 (+/-13.8) years in the Avazzia BEST group and mean age of 54 (+/-15.6) years in the Placebo group. As for gender, 8 (40%) were males and 12 (60%) females. Ethnicity of patients in this study is divided into Indian 11 (55%) and non-Indian 9 (45%) (Table 1).

Pain severity based on numerical rating scale, was expressed in median as 7.5 (pre treatment) and 3.5 (post treatment) for Avazzia BEST group, and 5.0 (pre treatment) and 4.5 (post treatment) for the Placebo group (Table 4). No patient was dropped out of this study.

Table 1: Patient Baseline Characteristics

DEMOGRAPHICS	AVAZZIA BEST	PLACEBO	P value
Age	53.5 (+/-13.8)	54.0 (+/-15.6)	0.746*
Gender			
Male	6	2	
Female	4	8	0.17**
Ethnicity			
Indian	6	5	
Non-Indian	4	5	1**

*T-test
**Fisher Exact Test

Table 1 showed that patients from both arms are in a mean age between 50-55 years old. The ethnicity of the patients recruited is divided into Indian and Non-Indian group to make data better distributed. The patients' baseline data from both arms were statistically similar as depicted by their P values.

Table 2: Patients' Diagnoses

DIAGNOSIS	AVAZZIA BEST	PLACEBO
Lower Back Pain*	5	5
Neck Pain**	1	1
Upper Limb Pain***	1	1
Lower Limb Pain****	0	1
CRPS	3	1
Fibromyalgia	0	1

*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 2 showed 6 main causes of chronic neuropathic pain in these patients, with majority suffered from lower back pain which includes degenerative spine disease, prolapsed intervertebral disc or spinal stenosis.

Table 3: Medications taken by the patients

MEDICATIONS		AVAZZIA BEST	PLACEBO	P VALUE
PARACETAMOL	YES	3	3	
	NO	7	7	1**
NSAIDS	YES	5	3	
	NO	5	7	1**
OPIOIDS	YES	6	7	
	NO	4	3	1**
GABAPENTINOIDS	YES	6	6	
	NO	4	4	1**
ANTI DEPRESSANT	YES	1	3	
	NO	9	7	0.582**

* T-test
** Fisher-Exact Test

Table 3 showed that the pharmacological treatment modalities for all patients recruited were statistically similar as depicted in P values. Most patients are taking at least three to four types of medications listed above for their chronic pain.

Table 4: Perceived pain level based on numerical rating scale

	AVAZZIA BEST	**PLACEBO**
PAIN SCORE		
Before treatment	7.5 (4.5)	5 (2.75)
After treatment	3.5 (4.5)	4.5 (4.25)
P value*	0.005	0.039

All data are in median (interquartile range).
*P value is obtained via Wilcoxon Signed Rank Test.

Pain score in both arms showed statistically significant reduction as indicated by the P-value of 0.005 and 0.039.

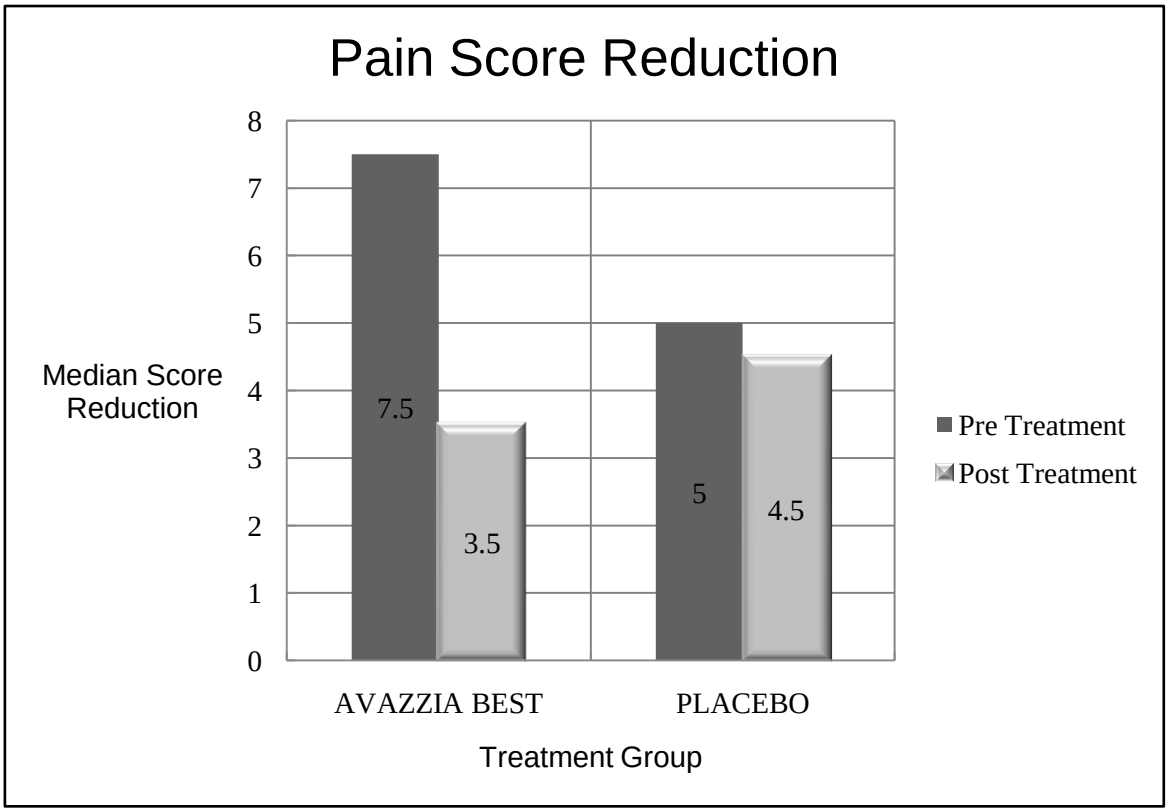
Table 5: Pain Biomarkers Level Before and After Treatment

	CORTISOL	**β–ENDORPHIN**	**TNF ALPHA**
AVAZZIA BEST			
Before treatment	219.5 (189.5)	210.5 (101)	8.25 (2.9)
After treatment	170 (121.5)	167 (111.75)	7.45 (4.05)
P value*	0.013	0.028	0.386
PLACEBO			
Before treatment	281.5 (171.25)	238 (245.5)	7.9 (5.725)
After treatment	273.5 (198)	154 (201)	7.72 (2.925)
P value*	0.074	0.007	0.959

All data are expressed in median (interquartile range).
*P value is obtained by Wilcoxon Signed Rank Test.

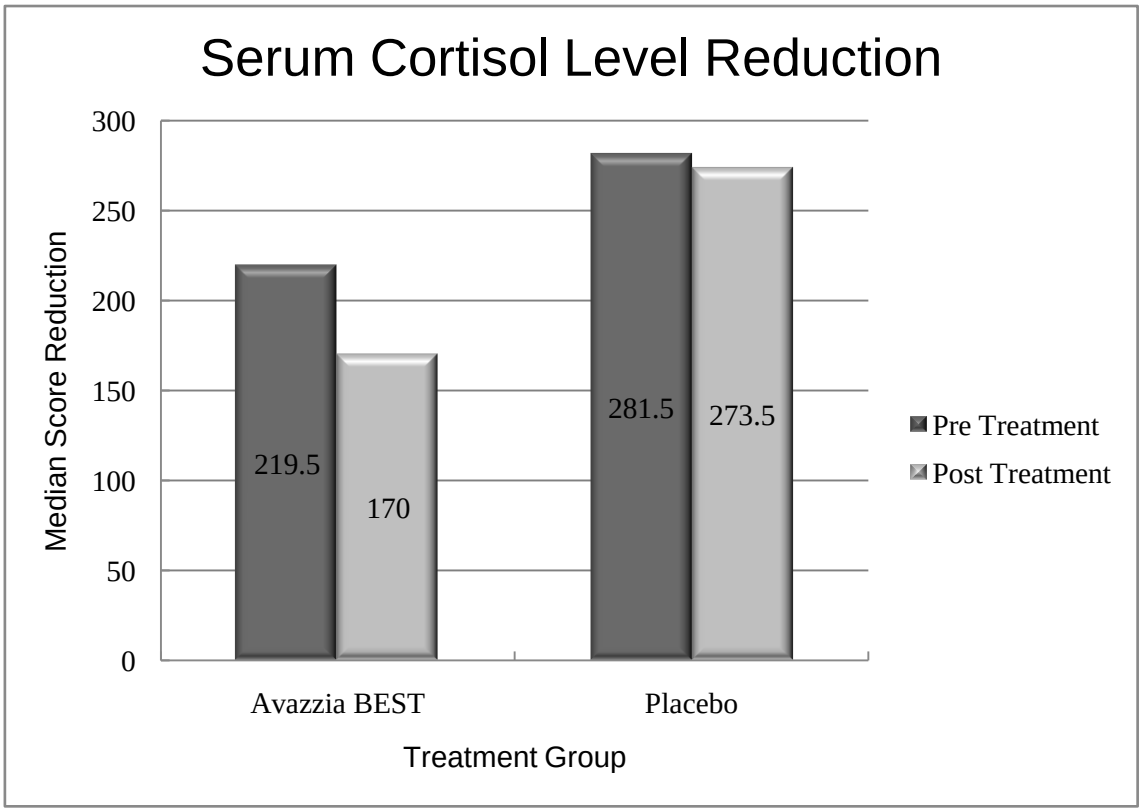
Both Avazzia BEST and Placebo group showed reduction in serum cortisol level post treatment, but the drop in the former was statistically significant as shown by a P value of 0.013. In both groups, the reduction in serum TNF-α level were not statistically significant (p value 0.384 and 0.959), where as in serum β-endorphin level, the reduction (which is contrary) was somehow statistically significant.

Figure 1



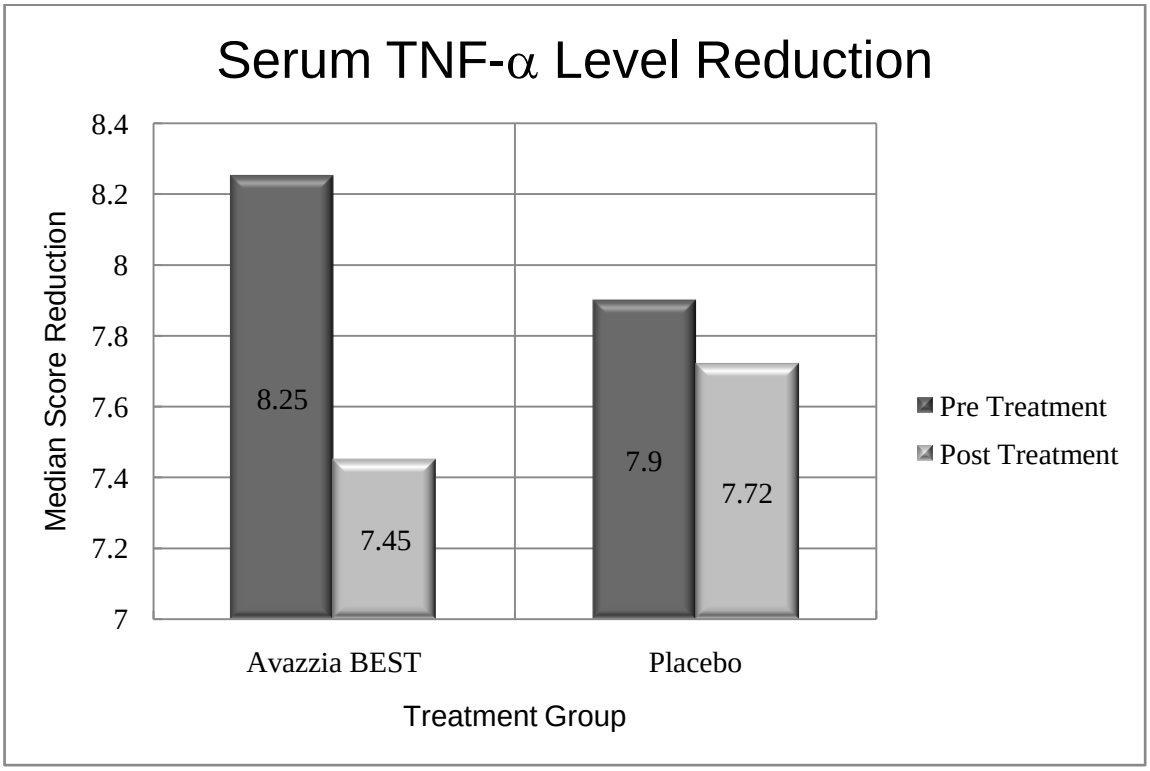
The median pain score reduction was statistically significant for both group of patients treated with Avazzia BEST (P value 0.005), and Placebo (P value 0.039). However, the Avazzia BEST treatment group shows a more significant drop in pain score after a single session of treatment.

Figure 2



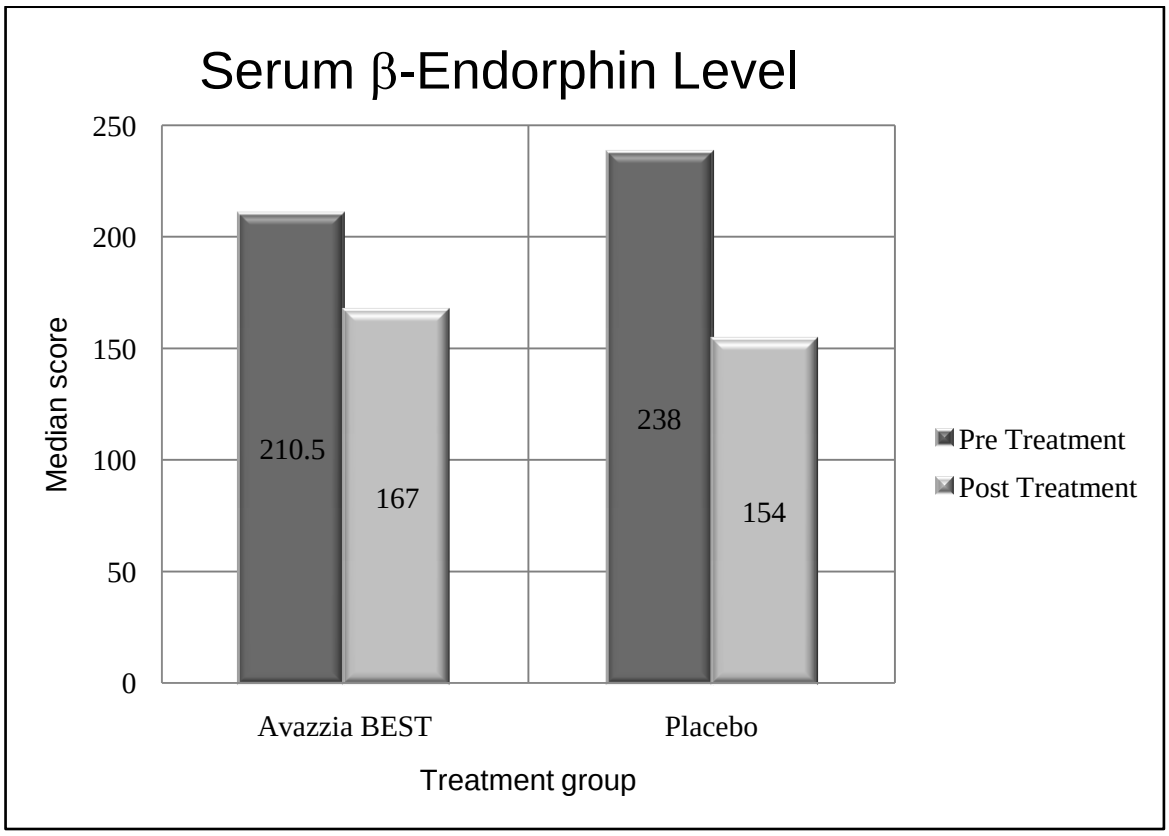
There is a drop in the serum cortisol level in both group post treatment, however, only the Avazzia Best group showed a statistically significant drop as depicted by its P value 0.013.

Figure 3



Median score reduction for serum TNF-α level in both Avazzia BEST and Placebo group post treatment was not statistically significant as shown in their P values of 0.386 and 0.959.

Figure 4



There is a statistically significant drop in serum β-endorphin level in both treatment group as depicted in their P-values of 0.028 (Avazzia BEST) and 0.007 (Placebo).

4. DISCUSSION

Pain is an individual and subjective experience modulated by its psychological, physiological and environmental factors. The definition of pain underlies the complexity of its measurement and management. Neuropathic pain is defined by the IASP as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system[1, 2]. It is a recognized type of pathological pain where nociceptive responses persist beyond the resolution of damage to the nerve or its surrounding tissue. Very often, neuropathic pain is disproportionately enhanced in intensity (hyperalgesia) or altered in modality (hyperpathia or allodynia) in relation to the stimuli. To date, there is as yet no common consensus about the etiology of neuropathic pain. The possible mechanisms can be categorized into peripheral sensitization and central sensitization of the nervous system in response to the nociceptive stimuli[4].

Neuropathic pain is among the most difficult types of chronic pain to treat which not only significantly impairs patients' quality of life [5] but also adds to the burden of direct and indirect medical cost for our society [5, 6]. Management of neuropathic pain is complex, and involved multidisciplinary approach. The discovery of new inhibitors or modulators of the production of cytokines represents a new possibility of clinical treatment, since current treatment options are limited. Researchers have examined a great number of pain biomarkers, but none have yet to be validated. Nonetheless, many studies have reported interesting findings correlating intensity of chronic pain with altered levels of circulatory biomarkers.

In the last decade, an increasing number of pain clinicians are integrating electrostimulation therapy into their clinical practice, complementing pharmacological treatment because it is non-invasive, has fewer side effects and produce simultaneous analgesic effects, though temporary, in chronic pain patients. Avazzia BEST is the latest design of electro-stimulation device under the umbrella of TENS- like devices, with emphasis on the problem of chronic pain. Till date, many clinicians are still unfamiliar with the considerable scientific evidence demonstrating the efficacy of Avazzia BEST device. This study aim to evaluate the effect of Avazzia BEST technology to changes in pain biomarkers (eg. serum TNF-α, cortisol and β-endorphin levels) in chronic neuropathic patients following a single dose treatment.

4.1 CORTISOL

Cortisol is an end product of HPA stimulation. This axis is stimulated by any inflammatory, emotional, or physical stress[17]. There is no greater stress than pain, and chronic pain may be accompanied by neuroinflammation [18]. When pain occurs, the axis is stimulated, causing CRH, ACTH, catecholamines, and serum cortisol to rise [19]. When acute pain turns chronic, the stimulation of the HPA axis continues, resulting in elevated serum cortisol levels[20, 21]. The natural purpose of elevated cortisol is activation of the body's immune defenses and healing to eliminate the cause of pain and facilitate tissue recovery [22].

The relationship between pain and high serum cortisol levels is unclear and complicated. Variability is seen in the hypothalamic-pituitary response to chronic pain, which is best explained by the time course of pain and the great variations in the neuroinflammation and neuroplasticity of chronic pain [23]. Despite variability in pain causation and varying effects of chronic pain on the axis, the effects of chronic pain on adrenal gland show a rather consistent pattern. . Serum cortisol concentrations that are too high or too low are biologic markers that call for aggressive pain management to bring the cortisol level into normal range. Serum cortisol should be viewed as an essential biologic marker for adequate pain control.

A statistically significant reduction in serum cortisol level (P value 0.013) was observed after a single session of Avazzia BEST treatment (Table 4). Although there is a strong link between cortisol and pain, there is so far no study to date to evaluate the effect of electrostimulation therapy to serum cortisol level in chronic neuropathic pain patients. However, the relationship between electrostimulation therapy and serum cortisol level had been studied in the past in the treatment of some psychiatric disorders. Daniel L. Kirsch et al advocates that cranial electrotherapy stimulation (CES) increased blood plasma level of B-endorphin, adrenocorticotrophic hormone (ACTH), serotonin, melatonin, norepinephrine and cholinesterase, and also decreased serum cortisol levels [24]. CES treatments are cumulative; however, most patients show at least some improvement after the first treatment. CES uses medical devices about the size of a cell phone that send a pulsed, weak electrical current (<4 mA) to the brain via electrodes placed on the ear lobes, maxilla-occipital junction, mastoid processes, or temples.

In present study, the serum cortisol level in the Placebo group observed a non-statistically significant drop (p value 0.074) post treatment session. Application of sham Avazzia BEST probe in the form of massage over pain site of patients may have produced some degree of relaxation. Tiffany Field et al suggest the stress-alleviating effects (decreased cortisol) and the activating effects (increased serotonin and dopamine) of massage therapy on a variety of medical conditions and stress experience [25].

4.2 TUMOUR NECROSIS FACTOR- ALPHA (TNF-α)

Recent studies that have established the relationship between neuroimmune function and nociception are focused on understanding the role of cytokines, chemokines, and neurotrophins on the development and maintenance of chronic pain syndromes, especially neuropathic pain [7-9]. Neuropathic pain has many features of neuroimmune disorder being modulated by immune cells that release cytokines. IL-6 and TNF-α are commonly involved in the inflammatory response resulting from spinal cord injury on animal[10]. Animal models of neuropathic pain based on various types of nerve injuries (peripheral versus spinal nerve, ligation versus chronic constrictive injury) have persistently implicated a pivotal role for TNF-α at both peripheral and central levels of sensitization[4].

TNF-α is the prototype pro-inflammatory cytokine that is involved in the maintenance of inflammation and development of neuropathic pain due to its ability of direct activation of signal transducers, receptors, and channels in nociceptive afferent fibers and other cytokines, neurotrophic factors, bradykinin, and the neurovegetative system, and of changing synaptic plasticity into a state of long-term facilitation [11,12]. The roles of TNF-α in neuropathic pain induced by nerve injury is recognized at different levels of the nervous system: (i) at site of nerve injury; (ii) at dorsal root ganglion; (iii) at dorsal horn of the spinal cord; and (iv) at the brain and higher centres [4]. The mechanisms by which TNF-α elicits pain behavior are still incompletely understood. Numerous studies suggest that TNF-α may increase excitability of primary afferent neurons via increased currents through sodium or calcium channels, a reduction of currents through potassium channels or a combination of any of these possibilities [13].

Myers et al advocates TNF-α as the best biomarker for painful changes in the nerves and dorsal root ganglion [14]. It has been implicated in the pathogenesis of multiple sclerosis, HIV neurological diseases and peripheral demyelinating neuropathy. TNF-α level were significantly higher in patients with chronic back pain compared to control in a 6months follow up study [15]. Many studies have demonstrated that local or spinal administration of agents that antagonize TNF-α will attenuate pain behaviors in neuropathic animal models. This intricate link of TNF-α with other neuro-inflammatory signaling systems (e.g. chemokines and p38 MAPK) has inspired a perspective for future drug development in treating neuropathic pain.

Carolyn et al implicates that cytokines changes occur in microcurrent treatment for fibromyalgia associated with cervical spine trauma. A significant reduction of cytokines (e.g. TNF-α, Interleukin-1, Interleukin-6 and substance P level) post treatment with subjective improvement in pain score were observed[16]. In present study, Avazzia BEST group showed a reduction in serum TNF-α level from 8.25 (before treatment) to 7.45 (post treatment) but the drop was statistically not significant (P value 0.386). This can be possibly explained by the small sample size in this study.

4.3 BETA ENDORPHIN (β -Endorphin)

Endogenous opioid peptides are ligands that bind to peripheral opioid receptors during painful inflammations or neuropathy. Endorphin and enkephalin have shown to play leading role in pain inhibition [26]. β-Endorphin, a 31-amino-acid peptide, is primarily synthesized in the anterior pituitary gland and cleaved from pro-opiomelanocortin, its larger precursor molecule [27]. β-Endorphin can be released into the circulation from the pituitary gland or can project into areas of the brain through nerve fibers.

Animal model experiment had demonstrated electropuncture treatment resulting in reduction of cancer pain which correlated to decrease in subtance P and increase in β-endorphin [28]. Stagg et al showed evidence that regular moderate exercise can induce sustained release of endogenous opioids in the brain cerebrospinal fluid and sustained relief from neuropathic pain in animal model [29].The increased β–endorphin level post exercise was able to be reversed with opioid receptor antagonist such as naloxone. This outcome suggests that endogenous opioids can be used as pain biomarkers since its up-regulation is strongly associated with reduction in pain.

Electrostimulation therapy is a non-pharmacologic method of pain relief accompanied or mediated by β-endorphin release. Following administration of high frequency TENS in human subjects, study has found that there was a time dependent increase in concentrations of β-endorphins in the circulation and cerebrospinal fluids [30]. Gabis et al studied on 20 chronic back pain patients which revealed an increased in β-endorphin level post transcranial electrostimulation therapy [31]. In another study of 31 healthy volunteers by George et al, outcome supports the hypothesis that TENS analgesia is mediated by the increase in β-endorphin. In addition, a relationship was demonstrated between increased β-endorphin levels and an increase in the pain threshold as measured by the evoked potential response [32].

In our study, however, serum β-endorphin level in both Avazzia BEST (P value 0.028) and Placebo (P value 0.007) group had shown a statistically significant reduction from pre to post-treatment level. This observation can possibly be explained by the presence of confounding factors such as opioid medications or delay in processing blood samples after treatment. The effect of pharmacological medications, particularly opioids that the patients are regularly taking may affect the release of β-endorphin.

In addition, bloods collected pre- and post- treatment were not immediately, but only analyzed with the ELISA kit much later. Hence, this may have affected the post treatment results. Foleys et al studied the pharmacokinetics and the hormonal, analgesic and behavioral effects of human β-endorphin after intravenous and intra-cerebroventricular to patients [33]. The outcome revealed that the mean terminal half-life after intravenous administration of 5 or 10 mg of human beta-endorphin was 37 min, and the half-life of beta-endorphin in cerebrospinal fluid after intra-cerebroventricular administration was 93 min.

Another postulation is the possible defective endogenous pain control system in our patients. Emmanuel et al speculated that low CSF β-endorphin found in patients with chronic neuropathic pain due to trauma or surgery could indicate an insufficient production of CSF β-endorphin by hypothalamic neurons, resulting in defective top-down modulation (eg. via the PAG-RVM system) of inputs from the periphery [34].

4.4 Limitations and Recommendations

Firstly, we recognized that the sample size for this study is small, consisting only 20 patients. As we had only about 6 months for recruitment of patients, this random number of 20 was taken. Hence, power of study was not calculated, and outcomes of this study maybe inadequate. In future study, it should span over a longer period of time, and power analysis should be used to calculate minimum sample size required so that one can reasonably likely to detect an effect of a given size.

Secondly, this study provides only a single session of treatment without any follow up on these patients post treatment, thus any changes in pain biomarkers which correlate with improvement in perceived pain levels may be of limited benefits in clinical practice. The long term analgesic effect of Avazzia BEST in chronic neuropathic pain patients is yet to be elucidated although there is a promising outcome from this study. Hence, a future study on this device should involve more than one session of treatment with subsequent follow up to review long term pain relief effect, which will definitely add value to this present study.

Lastly, we observed that the time taken to process and analyze the blood samples obtained with ELISA kit has been too long. Therefore, the outcomes of changes in pain biomarkers both pre and post treatment maybe affected and not accurate. In future study, this factor should be standardized to yield significant results.

5. CONCLUSION

Avazzia BEST technology demonstrated a marked improvement in perceived pain level based on numerical rating scale with a significant reduction in serum cortisol level after single dose treatment. A drop in serum TNF-α level was also observed, though not statistically significant. There is no correlation between the serum β-endorphin level and Avazzia BEST in this study. The long term efficacy of this device in correlation with changes in pain biomarkers is therefore yet to be elucidated.

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