Comparing Percutaneous Electrical Neuro-Stimulation with Placebo in the Management of Diabetic Peripheral Neuropathic Pain

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Abstract

Painful diabetic neuropathy is a common phenotype of peripheral neuropathy due to diabetes, affecting up to a third of the general diabetic population. The aim of this study was to evaluate the efficacy of auricular percutaneous electrical neuro-stimulation (PENS) in treating and relieving patients suffering from painful complications of diabetes.

A double-blind, randomized, placebo-controlled longitudinal trial enrolled 89 subjects with pain due to peripheral neuropathy caused by type 2 diabetes mellitus. Patients with pain duration of 4 months involving the lower extremities were randomly assigned to receive either standard (A) or variable-frequency (B) auricular PENS treatment, or a sham device, for 12 weeks, on a week-on week-off basis. Visual analogue scale (VAS) on 10 cm was used to assess pain, while severity of peripheral neuropathy was estimated through the vibration perception test (VPT) and the overall neuropathy limitation scale (ONLS). Insomnia and anxiety/mood severities were appraised by means of, respectively, the insomnia severity index (ISI) and the Hamilton anxiety rating scale (HAS). These 5 measures were repeated each week, alternating between installation and removal of the treatment device. Patients were encouraged to come back and complete the 6 treatments. Parameters of diabetic control were gauged at the first and last visit.

Population size dwindled from initial 89 to 63 subjects remaining after 12 weeks (21 with A, 22 with B). VAS, VPT, ONLS and HAS measures decreased with statistical significance for all 43 individuals in comparison with 20 placebo-treated patients (p-value $\ll 0.001$). Pain scores were found to linearly reduce with time from 7.1 ± 0.6 to 6.5 ± 1.0 over the complete study period with placebo, whereas neurostimulation allowed reductions from 7.2 ± 1.0 to 4.5 ± 1.0. Moderate pain VAS drops were found to be accompanied by drastic plunges in VPT. Study subjects were further sieved according to the decrease of blood glucose measures. Patients who demonstrated good glycemic control (16 out of 43) had quadratic reductions in pain with treatments A and B, from 7.5 ± 0.9 to 4.1 ± 0.6, and from 7.1 ± 1.3 to 3.2 ± 0.7, respectively. Glycemia also determined the decline of anxiety scores. Furthermore, ISI exhibited overall significant decrease ($p \ll 0.001$) for PENS groups in comparison with a raise of insomnia values for the control group. Analgesic requirements decreased by 80% for both treatment groups and only by 7% with placebo. No adverse events were found.

Active PENS treatments improved the neuropathic pain symptoms in all patients who completed the 12 weeks. Their resilience in participating may explain this success. In addition to decreased extremity pain, PENS improved physical activity, sense of well-being, and sleep quality while reducing the need for analgesics.

Keywords:
Diabetic Neuropathy, Painful, Percutaneous Electrical Neuromodulation; MeSH IDs D003919, D004561

1. Introduction

With 371 million people diagnosed with diabetes mellitus worldwide and a prevalence of 8.3% as per the 2012 Diabetes Atlas, diabetes mellitus has become a global burden [1]. This pandemic mostly relates to type 2 diabetes mellitus, which remains asymptomatic in many patients for a prolonged duration, and is diagnosed only with the emergence of associated complications [2]. Diabetic peripheral neuropathy (DPN) is a well-known microvascular complication of type 2 diabetes mellitus attributed to chronic hyperglycemia, and is defined as the presence of peripheral nerve dysfunction in diabetics after exclusion of other causes [4, 5, 6]. Approximately 40–50% of the patients developing DPN further develop painful DPN. Neuropathy and neuropathic pain are among the strongest determinants of reduced health-related quality of life in patients with type 2 diabetes mellitus. It has been reported that excess healthcare costs attributed to the management of DPN can lie in the range of $1,600–7,000, and painful DPN management can increase the cost of treatment up to threefold. Apart from the direct costs involved, DPN can also lead to work absence, change in employment and disability [7].

Management of diabetic peripheral neuropathy consists of

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strict control of diabetes and treatment of neuropathic pain using topical agents such as capsaicin cream and lidocaine patches, tricyclic antidepressants such as amytriptyline, nortriptyline or desipramine. Anticonvulsants such as gabapentin, pregabalin are typically employed, with others like mexiletine, tramadolol, dextromethorphan and narcotic analgesics (oxycodone, levorphanol). However, the non-pharmacological treatment only consists of relaxation techniques (meditation, yoga), biofeedback, hypnosis, low intensity transcutaneous electric nerve stimulation (TENS), acupuncture and henna application to the feet, techniques which have provided variable relief from neuropathic pain in diabetic patients [8, 9].

Compared to the manual acupuncture, the neuro-stimulation of cranial nerves is considered to increase the medical efficacy. Percutaneous electrical nerve stimulation (PENS) therapy was seen as promising for improving the glycemic profile in obese and type-2 diabetic patients [10], post-herpetic trigeminal neuropathy [11], headaches disorders [12, 13, 14], traumatic and vascular diseases [15]. However, no clinical studies hitherto reported the involvement of auricular PENS for treating diabetic peripheral neuropathy. Hamza *et al.* [3] hinted to a PENS therapy which stimulated sensory nerves at the level of the lower limbs where pain is most felt. Still and all, the impracticality of their procedure, the failure to monitor blood glucose levels or biothesiometry. and the importance of maintaining the stimulation for a sustained effect, stressed the need for testing a wearable device using objective measures. We planned to study and evaluate the effectiveness of continuous auricular PENS therapy as an outpatient treatment of conditions associated with peripheral neuropathy in type-2 diabetic patients.

2. Materials & Methods

We used First Relief™ (DyAnsys Inc., San Mateo, CA), a miniaturized PENS device (measuring about 6 x 2 cm) designed to administer intermittent electrical auricular neurostimulation via selectively placed needles in ambulant patients (Figure 1).

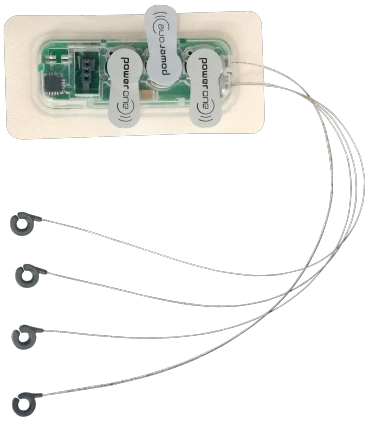

Figure 1: PENS battery-operated device with three electrodes.

This battery powered base unit was placed behind the pinna, and the site of placement of micro needles was identified using a nerve locator provided by the manufacturer. Needle insertion points were chosen by highlighting places of least resistance in the proximity of the identified points using skin impedance. The conducting wires and needles were attached to the base unit as recommended. The manufacturer suggested usage of the device for alleviating signs and symptoms of peripheral neuropathy. Three auricular locations were recommended by the manufacturer, viz. Toes, Spinal Cord Sensory Neurons and the Cingulate Gyrus points (Figure 2).

Lead I : ATN LON Toes {E}
Lead II : LON Spinal Cord Sensory Neurons
Lead III : ABVN ATN Cingulate Gyrus

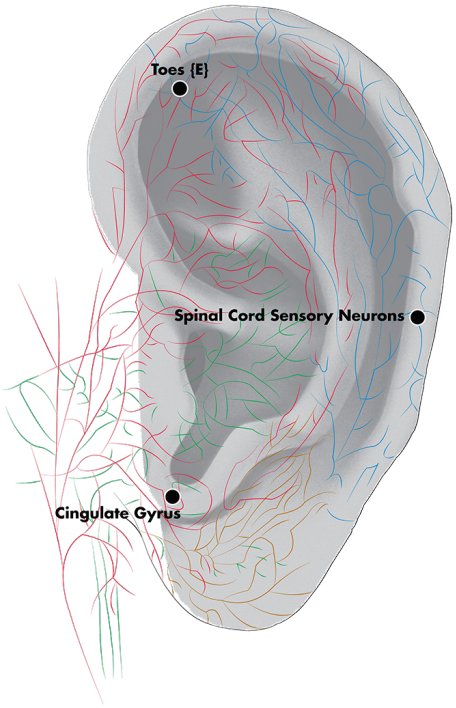

Figure 2: Placement of electrical stimulation (3 leads) on the human auricle.

The stimulation needles are placed at three specific points. This has the property of stimulating the cranial nerves in the human body, namely, the ATN, ABVN & LON nerves. The stimulus intensity is typically below the individual's pain threshold, yet above the lowest intensity that would evoke a tingling sensation. These low-level electrical pulses at the ear can be programmed according to various parameters (frequency, time duration, power and duty cycle). By default, the device emits a low voltage biphasic signal at 1 Hz frequency with a pulse width of 1 ms. This standard stimulation (A) can be extended to a sweep mode (B), ascending from 1.14 Hz for 1 second, to 2.28, 4.56 & 9.12 Hz for the subsequent 3 seconds, then descending back to 4.56, 2.28 & 1.14 Hz stimulations for another 3 seconds, reascending etc. The stimulation is on for 2 hours and off for 2 hours, this neuro-modulation continues over a time span of 7 days. We aimed at testing both modes, standard and sweep stimulation for relieving pain due to diabetic peripheral neuropathy.

After local institutional review board approval and following written informed consent, diabetic patients were enrolled in a prospective, randomized, parallel assignment, double blinded,

interventional, placebo controlled clinical trial. The study was registered on ClinicalTrials.gov under identifier NCT03540446. Screening data was reviewed to determine subject eligibility. The study was planned to be conducted for a period of four to six months, including a therapy period of 12 weeks (84 days) with 6 treatments, each treatment spanning 2 weeks (installation and follow up). The additional time taken was to define the characteristics of the patient population and to recruit appropriate patients. The first three months duration included screening, enrollment and recruitment of the subjects and later three months were scheduled for the participant follow-up. A control group C was also defined where subjects would receive a placebo (dummy device with no electrical stimulation) placed topically onto the backside of the ear.

Before initiating treatment modality, all patients were asked to record their baseline levels of pain, by using 10-cm visual analog scales (VAS), where 0 = minimal (lowest) and 10 = maximal (highest), limitations in the everyday activities of the upper and lower limbs by overall limitation neuropathy scale (ONLS) and quality of sleep by insomnia severity index (ISI). VAS evaluations of pain, physical activity, and sleep were performed before each treatment session, after each week of treatment, and again at the end of the 6-week treatment period with each modality.

Change from baseline in pain intensity scores, subjective assessments of diabetic peripheral neuropathy signs and symptoms, and their objective assessments using a biothesiometer were at the heart of the investigation (VPT and ONLS scores). In addition to examining the possibly acute analgesic effects of PENS, changes in physical activity, quality of sleep, and requirements for analgesic medication were recorded. Improvement in the mood levels were also considered with scores over the Hamilton anxiety scale (HAS).

The non-invasiveness of the device was expected to demonstrate no relevant incidence of adverse effects or events related to the test product. However, the patients were advised to inform about any uneasiness not limited to nausea, vomiting or headaches. Grievances of patients were duly recorded.

Inclusion criteria were as follows:

- Patients must be in the range from 18 to 75 years of age.
- Patients of either gender diagnosed with type 2 diabetes mellitus of any duration, established as per American Diabetes Association guidelines (random blood sugar > 200 mg/dL or fasting blood sugar > 126 mg/dL).
- Patients with known diabetes mellitus based on the duration of diabetes (≥ 5 years).
- Patients with complications of retinopathy, nephropathy and diabetic autonomic neuropathy.
- HbA1c ≤ 12 % (HbA1c ≥ 6.5 % regarded as chronic diabetes mellitus) at the time of screening.
- Diabetic neuropathic pain is based on the Toronto Expert Panel on diabetic neuropathy diagnostic criteria that include positive neuropathic sensory symptoms (e.g., "asleep numbness", "prickling" or "stabbing", "burning" or "aching" pain) predominantly in the toes, feet or legs for more than three months prior to screening and with no adequate relief from other treatments, or neuropathy disability score ≥ 6.
- Medications affecting peripheral nerve areas should be discontinued prior-to or during the study: NSAIDs, antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin or gabapentin and multivitamins.
- The diagnosis of diabetic peripheral neuropathy can only be made after a careful clinical examination, and all patients with diabetes should be screened for peripheral neuropathy by examining
  - Pressure sensation using 10g (5.07) monofilament at 4 of the 10 standard sites of the sole of the feet (plantar base of the big toe, 2nd and 5th toes and at the heel), avoiding areas with callosity.
  - Vibration perception threshold using biothesiometer.
  - Pain perception by the application of pin prick on the proximal part of the great toe (to barely depress skin) is positively classified when the patient could distinguish sharpness or negatively when the patient could not distinguish it.
  - Achilles deep tendon reflex using standard patellar hammer.
- Patients present an average pain score of ≥ 5 for 24 hours at least four days out of the week prior to randomization as assessed by Brief Pain Inventory and Visual Analog Scale for pain.
- Patients understand and are willing to participate in the clinical study and can comply with study procedures and visits.
- Normal cognitive and communicative ability as judged by clinical assessment and ability to complete self-reported questionnaires.

Exclusion criteria were as follows:

- Evidence of another type of neuropathic pain caused by a condition other than diabetes.
- Absolute numbness which would suggest nerve damage at a level where PENS therapy is unlikely to work.
- BMI (Body Mass Index) > 37 kg/m^2.
- Clinical signs of infection related to sores of any type on the legs.
- Subjects on any investigational drug or therapeutic device within 30 days preceding screening.
- Double participation in the two phases of this study.

- History of drug or alcohol abuse or smoking habit.
- Malignant disease not in remission for at least five years.
- Presence of one or more medical conditions which seriously compromises the subject's ability to complete the study, including history of poor adherence with medical treatment, unstable pain intensity or pain medications 6 weeks prior to the study, renal, hepatic, hematologic, active auto-immune or immune diseases, one or more abnormal blood biochemistry result $\geq$ 3 times that of the upper limit of the normal range.
- Known history of AIDS or infection with HIV.
- American Heart Association Class III and IV congestive heart failure, as defined by the following criteria:
  - Class III: Symptoms with moderate exertion
  - Class IV: Symptoms at rest
- Pregnant or breast feeding.
- Subjects with a diagnosis of psychiatric disorders such as major depressive disorder, bipolar disorder, obsessive compulsive disorder, generalized anxiety, dysthymia or suicide ideation.
- Administration of local anesthetic shot or systemic steroids within two months of screening.
- Subjects not willing to undergo a six-weeks treatments which include periods with non-pharmacologic pain management techniques.

In agreement with the objectives of the study, the identity of test and control treatments were not known to investigators, research staff, or patients. The procedures in place to ensure double-blind administration of the study included: strictly controlled access to the randomization product serial numbers, identical packaging and labeling of standard, sweep stimulations and placebo treatments.

The biothesiometry device was used to measure the threshold of appreciation of vibration in patients. A decreased sensitivity to these vibrations was understood to indicate the presence of a sensory neuropathy in diabetic patients. This is a quantitative measure of the vibratory sense of the peripheral neuropathy. The biothesiometer vibrates at a known frequency, and it is compared to other parts of the body with known vibration thresholds. The effectiveness of this test in documenting sensory neuropathy is considered as a useful screening test. It is worth noting that this is only assessing sensory nerve function (and not motor or autonomic nerve integrity) in association with diabetic peripheral neuropathy complications.

Blood glucose measures were taken at the first and at the last visit, estimating glycated hemoglobin (HbA1c), fasting blood glucose, and random postprandial blood glucose which really counts as capillary blood glucose (CBG). We proposed to investigate the role played by glycemic control in the efficacy of PENS.

Both descriptive and inductive statistics were applied to the obtained data. For the former, 95% confidence intervals were used, giving comparable indications of scores' ranges, together with averages and their deviations from the mean when considering the fabric of the populations (BMI, age) or providing shorthand sketches of the data. Score-time connected-dots graphs were devised, privileging comprehensiveness over succinctness. For the sake of discussion, least square error fits were provided, further illustrating the nature of growths or descents (linear, quadratic,...). All comparisons were appreciated using inferential tests (Mann-Whitney U, Kolmogorov-Smirnov) of the respective null hypothesis, giving asymptotic significance probabilities (p-values). R (R Foundation for Statistical Computing) and Mathematica (Wolfram Research, Champaign, IL) programming languages were employed for the data analysis, illustrations and visualizations.

3. Results

Though the subjects were chosen according to their potential to commit to all 6 treatments, throughout the 12 weeks only 63 subjects stayed to complete the full therapy, 20 in the control group, 21 and 22 with treatment modalities A & B. Out of the 20 final controls, the randomization process attributed 10 female and 10 male subjects. For the subjects who underwent neuro-stimulation, we obtained 25 male and 18 female subjects. It appears that this near-three months period isolated the subjects for which a positive change would take place. Indeed, all 63 remaining subjects showed significant improvement of their condition, with significant reduction of pain and peripheral neuropathy scores (see Table 1). In the course of time, subjects receiving inactive-devices saw a minimal reduction of pain, from an average pain VAS score of 7.1 to a final 6.5. However this modest improvement was not found in the peripheral neuropathy severity scores for controls.

In examining the blood glucose measures, we observed the existence of two distinct populations, that of good or poor glycemic control. We hereby defined good control by a decrease of CBG $\geq$ 65 mg/dl and if not, by a decrease of HbA1c $\geq$ 1.9%. 16 study cases (out of 43) were found conforming to this definition of good control, whereas all subjects in group C had poor control of their blood glucose. Using the Kolmogorov-Smirnov statistic (*cf* Appendix A), we further confirmed that this distinction according to diabetic parameters was natural in the study population, at the level of the first and last visits, respectively for postprandial blood glucose and glycated hemoglobyn. Notwithstanding the shared distribution for age values, the pain scores between the two diabetic outcomes did not adhere to the same statistical distribution, neither did the anxiety scores (*cf.* Table 2). BMI values also complied with such a differentiation, though at a slight statistical significance. Two separate populations thus co-existed. However, for analyzing VPT measurements, ONLS and insomnia scores, we resorted to the usage of the full study population as glycemia made there no difference in the underlying empirical distribution.

		Controls		Group A		Group B	
Gender		F (10/20)	M (10/20)	F (15/21)	M (6/21)	F (10/22)	M (12/22)
Age		54.7 ± 7.3		58.0 ± 6.8		58.1 ± 7.3	
BMI		23.6 ± 1.0		23.7 ± 1.2		23.4 ± 1.1	
Treatment		Before No. 1	After No. 6	Before No. 1	After No. 6	Before No. 1	After No. 6
VAS	Good GC	[6.8 – 7.4]	[6.0 – 6.9]	[6.7 – 8.4]	[3.5 – 4.7]	[6.1 – 8.1]	[2.6 – 3.7]
	Poor GC			[7.0 – 7.9]	[4.7 – 5.6]	[6.3 – 7.4]	[4.7 – 5.4]
VPT		[24.1 – 30.9]	[22.6 – 28.8]	[26.3 – 31.9]	[17.5 – 20.0]	[20.3 – 28.2]	[13.8 – 16.6]
ONLS		[3.4 – 4.0]	[3.4 – 4.1]	[2.7 – 3.4]	[1.0 –1.4]	[3.3 – 4.1]	[1.0 – 1.0]
Insomnia		[13.5 – 19.3]	[14.1 – 17.9]	[15.8 – 19.9]	[7.0 – 10.4]	[13.1 – 17.5]	[5.2 – 9.6]
HAS	Good GC	[12.5 – 13.5]	[10.1 – 11.9]	[8.8 – 13.0]	[4.2 – 7.8]	[6.5 – 12.4]	[3.8 – 5.8]
	Poor GC			[9.9 – 14.2]	[6.7 – 9.3]	[11.8 – 14.9]	[4.6 – 7.7]

Table 1: Results according to population groups and subgroups. [Average age and BMI are given with deviation from the mean; 95% confidence intervals were calculated for the various scores; GC denotes *glycemic control*.]

	Kolmogorov-Smirnov test p-value Comparing poor and good glycemic control	
	Age: $p > 0.3$	BMI: $p = 0.047$
	CBG (1st w.): $p < 0.001$	
	HbA1C (12th w.): $p < 0.001$	
VAS	$p \ll 0.001$	
VPT	$p = 0.97$	
ONLS	$p = 0.77$	
Insomnia	$p = 0.92$	
HAS	$p \ll 0.001$	

Table 2: Comparing data populations according to blood glucose control. See above for the exact conditions.

Differences of evolution of pain scores between the neuromodulation treatments and the placebo were found from the 3rd treatment onward. For the patients with good glycemic control, these differences became statistically significant after the 7th week, in the wake of the 3rd treatment. Overall we observed (see Figure 3) how the pain scores followed with time a small linear decrease for the placebo control group whereas these patients exhibited quadratic reduction when stimulation was actually applied. This latter relationship was found to match the following algebraic formulation (dashed trace in Figure 3):

$$\frac{1}{10} - \frac{e}{100}(16.3^2 - w^2),$$

where w is the week number, $e \approx \frac{87}{32} = 2.71875$.

Such a quadratic decline was seen for both treatments A and B. Nevertheless, subjects undergoing treatment B showed even greater diminution of pain scores than group A. Though these patients started in disarray, the full 12 weeks remarkably shuffled their pain levels and revealed the undergoing treatment, from lowest VAS values for group B with a maximum score of 3.4, higher scores for group A around 4, and pain scores invariably over 5 for the controls. Only two outliers were found to this quadratic pain score decent for subjects with good glycemic control (orange traces in Figure 3).

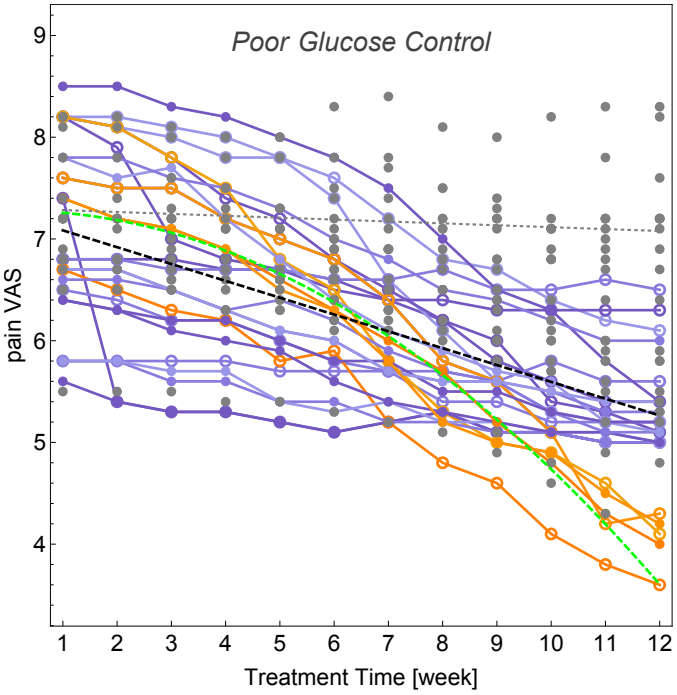

Figure 4: Pain scores over treatment time for subjects with poor glycemic control. [same legend applies from Figure 3, adding the black dashed fit, retaining the green dashed trace from the optimal study cases]

A steady linear decrease of pain VAS was found for subjects with poor glycemic control where it was deemed quadratic in the previous ideal cases, with a 9-fold rise in the slope magnitude ($\mu_{\Delta \mathrm{VAS}} = -0.17$, black dashed trace) from that which was observed for the controls ($\mu_{\Delta \mathrm{VAS}} = -0.019$, gray dotted trace). We theorize this existence of a small diminution of pain in the control group to the particular application of acupuncture via the needles of the dummy device, even without electrical stimulation. 5 cases (out of 27) were happy outliers, in that their pain score reduction resembled that which was found with better control of blood glucose levels (green trace in Figure 4 from Figure 3). We observe that HbA1C and glycemic levels were *in fine* controlled by the electrical stimulation (groups A and B), even when patients were not able to monitor their glycemic levels and adhere to their anti-diabetic medication. Such occur-

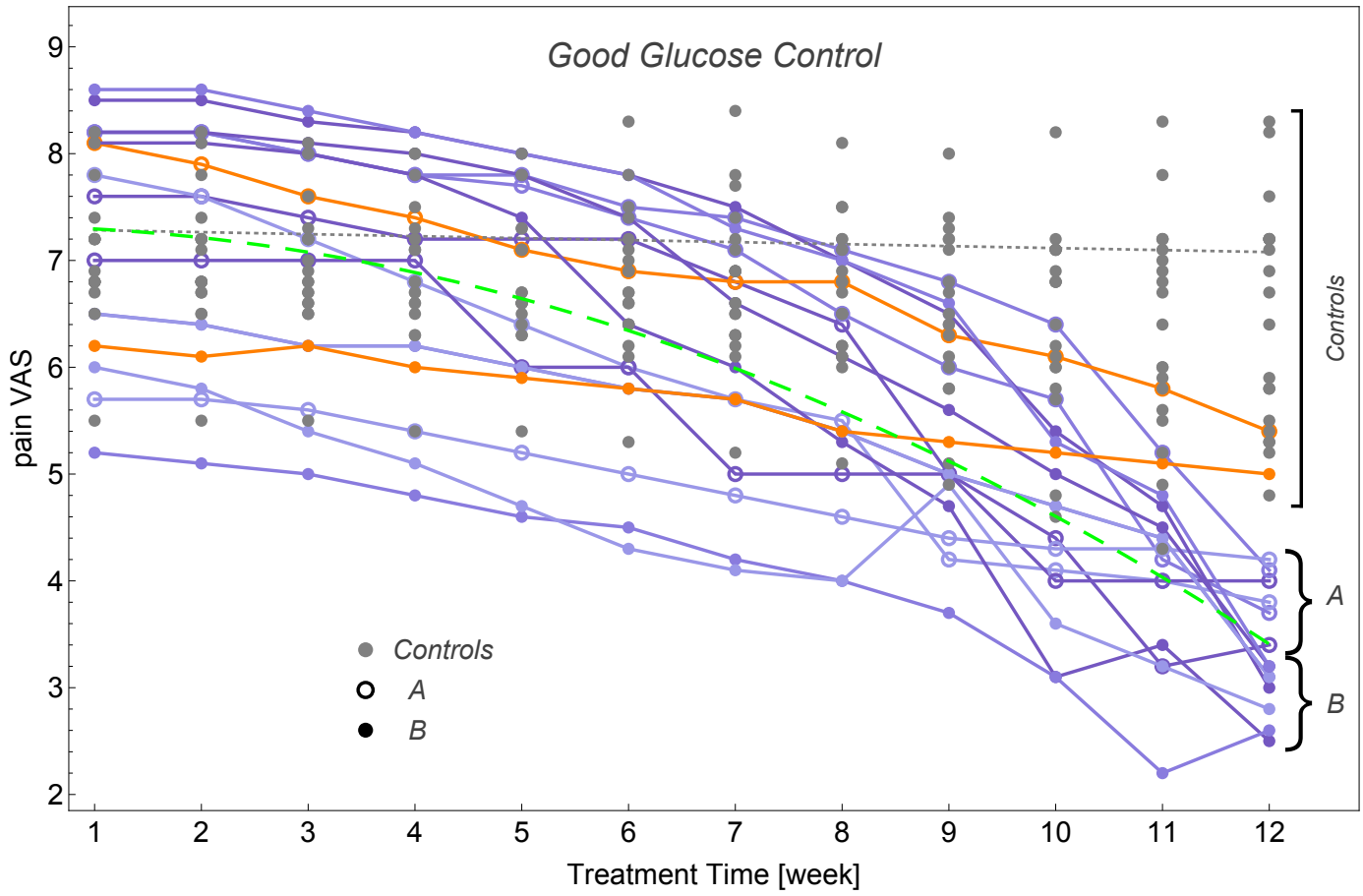

Figure 3: Pain scores over treatment time for subjects with good glycemic control. [Empty and full purple dots correspond respectively to treatments A & B; Gray full dots correspond to controls; Dotted and dashed traces correspond respectively to the fits for controls and for the optimal study cases]

rences were shared by the patients. Henceforth, it appears that acupuncture effect alone cannot alleviate the complications of diabetes peripheral neuropathy [20]. Poor pain VAS decrease often occurred with superior VPT decrease. This compensation was then systematically found with greater ONLS, ISI and HAS decreases.

Significant evidence of VPT scores decline was also observed, with no distinctions for sub-populations according to glycemia. Notwithstanding this widespread diminution, at the fourth week, in the onset of the second treatment, 3 patients undergoing treatment modality B saw a surge in VPT measures followed by a strong corrective decline during the third treatment.

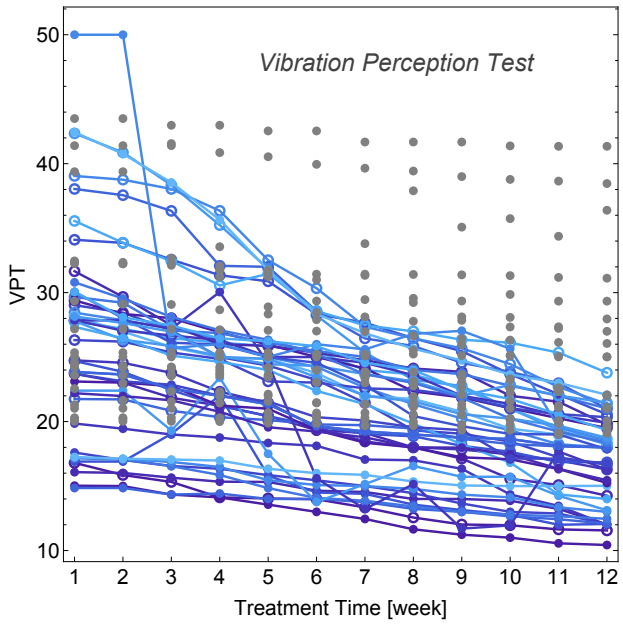

Figure 5: VPT scores over time. [Colored empty and full dots correspond respectively to treatments A & B; Gray full dots correspond to controls]

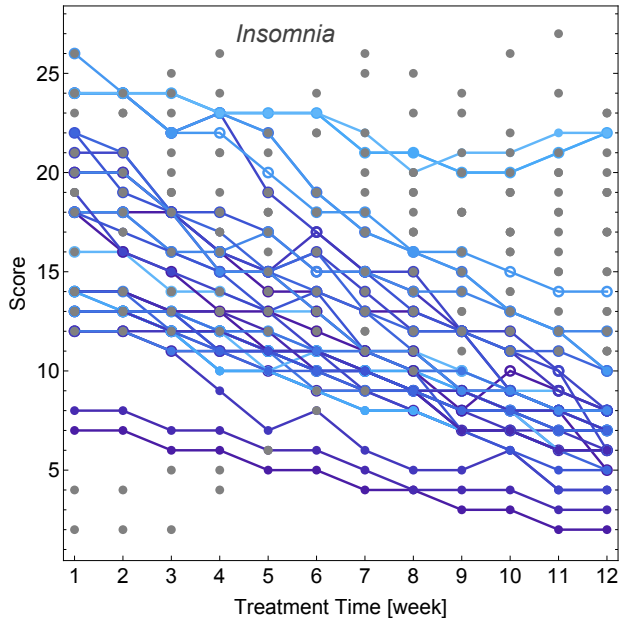

Figure 6: Insomnia scores over time. [same legend applies from Figure 5]

Insomnia only faintly increased on average for the controls while a significant decrease was seen for the subjects with neurostimulation (see Figure 6 and Table 1). We observed that the rate of change for pain was lesser than the rate of change for insomnia in the first 2 treatments. However pain decrease caught back later on, following the 4th treatment. Only three outliers (to the general decrease below 15 under neurostimulation) were found. They all started at a score of 24 and in finishing the 6 treatments ended with an ISI of 22. Of these exceptions, the one belonging to group A nonetheless exhibited the strongest diminution of VPT measurements (from 42 to 18).

This movement toward a healthier condition was corroborated by the anxiety scores, but group C also showed mood improvement nonetheless (last row of Table 1, Figure 7). On average, considerable decreases of diabetic parameters paralleled lower levels of anxiety. For group A, this meant a lower score throughout the 12 visits but for group B, the low scores matched nearly for 9 visits before the better glycemic cases plunged even lower on the Hamilton scale.

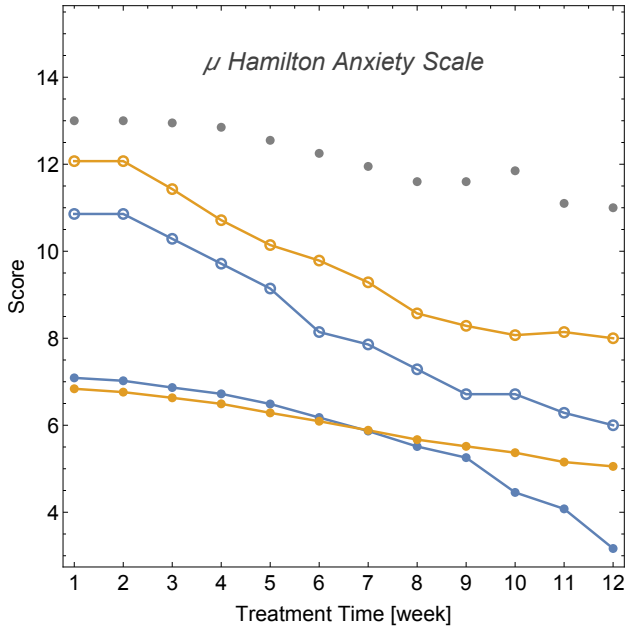

Figure 7: Mean HAS scores. [Yellow and blue traces respectively correspond to poor and good glycemic control, gray full dots to controls and colored empty/full dots respectively to A/B modalities]

4. Conclusion & Discussion

The longitudinal nature of the study over 12 weeks enabled a natural selection process seemingly based on the incentive for subjects to come back at the next visit. To our understanding, this would partially explain the 100% success rate according to pain reduction. Also, the mere decrease of pain scores for the controls also hints to the pain-reduction motivation of subjects in their resilience. Moreover, it became apparent that diabetic peripheral neuropathic pain is a great candidate for relief under auricular PENS treatment. Following the quadratic law we obtained for pain scores, it would appear that after 16 weeks, the pain levels should virtually approach zero, in the advantageous case of good glycemic control. Two more treatments

would have been necessary to test this new hypothesis of pain withdrawal.

A remarkable hindsight further emerged around the diabetic specificity of the study population. Though pregabalin and gabapentin medications were dropped following the inclusion of patients, the monitored scores invariably showed reduction over the full course of the study. This appears to hint at the elimination of the requirement for these two drugs, particularly under First Relief™ neuro-stimulation. Between the treatment groups and the controls, the decrease ratio for rescue analgesics was higher than 11:1.

The sweep stimulation modality (group B) reinforced the effect of neuro-stimulation and seems most appropriate for treating neuropathy. Concerning the effectiveness of the various modes of stimulation, one may argue that a frequency of 2 Hz works on the α, δ and μ receptors (enkephalins) while 100 Hz works on the κ receptors (dynorphins). It transpires that under treatment B the former neuropeptide regulated nociception in the body. The permanency of this regulated state should be investigated. We may have found first hints in the complaining of patients after removal of the device after the 2nd or 3rd treatments, a fact that contrasts with the lack of complaint after the 6th treatment. A year long followup may prove necessary to base this conclusion on the immutability of the neuromodulation benefits. Stimulating the brain with electrical currents results in the release of endogenous opioid peptides which induces analgesia [20] . We further defend the idea that chronic pain is due to the brain sending out wrong signals long after the original reason for the pain is gone. We hypothesize that with every treatment a form of neuroplasticity facilitates the attenuation of the wrong brain signals. It already appears that cumulative analgesic effects were here realized via this PENS repeatedly applied over multiple weeks.

The corroboration of patient reported outcomes by objective biothesiometry measures partially refuted the placebo hypothesis that advantages from the treatment were solely due to the participation of the subjects in the study or contact with a medical professional, or to the patients' sheer hopes.

Considering the simplicity of the procedure and in absence of side effects, it would be appropriate to use this auricular PENS as the primary treatment modality and supplement it with conventional pharmacological therapies as necessary.

Appendix A. Comparability of data

In order to compare two subpopulations from the study population, the Kolmogorov–Smirnov test was used, testing whether the two underlying one-dimensional probability distributions differ. The Kolmogorov–Smirnov statistic [17] is

$$D_{n,m} = \sup_x |F_{1,n}(x) - F_{2,m}(x)|,$$

where $F_{1,n}$ and $F_{2,m}$ are the empirical distribution functions of the first and the second sample respectively, and sup is the supremum function. The null hypothesis is rejected at level α if

$$D_{n,m} > \sqrt{-\frac{1}{2}\ln\alpha}\cdot\sqrt{\frac{n+m}{nm}}, \qquad \text{(A.1)}$$

where n and m are the sizes of first and second sample respectively. Tables of critical values were originally published [18], corresponding [19] to

$$c(\alpha) = \sqrt{-\frac{1}{2}\ln\alpha}$$

in the expression A.1 above. We chose cutoff $\alpha = 1/20$, giving us the condition

$$D_{n,m} > \sqrt{\left(\frac{1}{n}+\frac{1}{m}\right)\frac{\ln 20}{2}}$$

for determining the probability (i.e., p-value) that both samples were likely extracted from the same distribution.

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