

**THE EFFECT OF COMBINED LASERPUNCTURE
WITH PHARMACOLOGICAL TREATMENT FOR
REDUCING VAS SCORE, REDUCING IL-6 LEVEL,
INCREASING IL-10 LEVEL, AND IMPROVING
NERVE CONDUCTION VELOCITY IN PATIENTS
WITH DIABETIC NEUROPATHY OF THE
LOWER EXTREMITY**

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Keywords and phrases: laserpuncture, diabetic neuropathy, diabetes mellitus.
Received September 29, 2017

Abstract

The general complication in diabetic patients is painful and disadvantageous neuropathy. Treating diabetic neuropathy requires a correct timing in determining the therapy. Various modalities of treatment including pharmacological and non-pharmacological therapy is used in treating this disorder. The purpose of this study is to compare the effect of combined laserpuncture and pharmacological treatment; and combined *sham* laserpuncture with pharmacological treatment in patients with diabetic neuropathy. A randomized controlled clinical trial is done on 36 patients. Laserpuncture were applied on the MA-IC3 Endocrine ear acupuncture point, ST36 Zusanli, ST40 Fenglong, and SP6 Sanyinjiao bilaterally twice a week for twelve sessions; while in the control group, laserpuncture is done with the laser equipments turned off. The results showed a significant difference in the *mean* value of VAS score difference before and after treatment between the laserpuncture and pharmacology group and the *sham* laserpuncture and pharmacology group with the p value < 0.001 . The *mean* VAS score difference before and after treatment is -4.12 ± 1.204 in the intervention group and -1.37 ± 0.718 in the control group. There is no statistically significant difference in the *mean* difference of IL-6 level before and after treatment between the intervention group [-0.12 ($-2.04 - 17.66$)] and control group [-0.395 ($-17.28 - 5.33$)] with the p value = 0.318. There is a significant difference in the *mean* value of the increase in IL-10 before and after treatment between the laserpuncture and pharmacology group [0.05 ($-0.08 - 0.66$)] and the *sham* laserpuncture and pharmacology group [-0.075 ($-1.40 - 0.56$)] with the p value = 0.032; and in the increase of nerve conduction velocity of the left tibialis motoric nerve [0.00 ($-3.20 - 13.0$) and -2.35 ($-14.5 - 8.30$)] with the p value = 0.007.

Conclusion: The combined laserpuncture and pharmacology treatment is effective in reducing VAS score, increasing IL-10 level, and improve the nerve conduction velocity of the left tibialis motoric nerve in diabetic neuropathy patients; but is not effective in reducing the IL-6 level.

1. Introduction

Diabetic neuropathy (DN) is one of the most common chronic complication of Diabetes Mellitus (DM) [1], which affects up to 50% of DM type 1 and 2 patients [2, 3]. The risk involved in DM patients with DN are recurrent infection, unhealing ulcer, and/or foot amputation [1]. The incidence of DN increases in proportion to the length of time having DM and the increase in life expectancy [4].

The occurrence of DN is a series of processes that involved multiple factors, therefore the treatment or prevention of DN is actually a part of the management of DM in general. Until the writing of this study, besides a tight glycemic control, there had been no strong evidence of a therapy that can improve or prevent DN [1]. Nevertheless, to prevent the development or progression of complications, some pharmacologic and non-pharmacologic treatment can be done. The literature that discuss non-pharmacological therapy for DN is still very limited in number, of which studies that discuss acupuncture is one of the most commonly found literature [5]. Laserpuncture is one of the modalities of acupuncture that used laser light on the acupuncture points. The advantages of laserpuncture is painless and non-invasive.

2. Methods and Material

The study design used in this research is a randomized, controlled, double-blinded study. This study is done on April - June 2016 at the Metabolic Endocrine Polyclinic of the Internal Medicine Department RSUPN dr. Cipto Mangunkusumo, Central Jakarta. The obtainable population in this study are DN patients that visit the Metabolic Endocrine Polyclinic of the Internal Medicine Department RSUPN dr. Cipto Mangunkusumo, Central Jakarta and fulfill the inclusion and exclusion criteria. The inclusion criterias are patients having DM type 2, between 40-60 years of age, HbA 1c \leq 9%, the patients fulfill the diagnostic criteria of DN using the Diabetic Neuropathy Symptom (DNS) score and Diabetic Neuropathy Examination (DNE) score (score DNS $>$ 1 and DNE $>$ 3), VAS score before research \geq 4, and the patient signed an informed consent.

The exclusion criterias are patients having contraindication of laserpuncture, cancer patients, peripheral artery disease, liver / kidney disorder, pregnant, alcohol and substance abuse, nerve injury due to trauma, and radiculopathy. Patients using analgetics of the tricyclic antidepressant category (imipramine, amytriptilline, notriptilline),

serotonin-norepinephrine reuptake inhibitor (duloxetine, venlafaxine), antiepileptic drugs (gabapentine, pregabalin), and consuming herbal medicine for DM and pain. The sample size for this study after correction for the intervention and control group is 18 patients each.

The study subjects is allocated randomly using computer based random allocation method and concealment technique is used to avoid selection bias. Laserpuncture is a stimulation method using laser pen device with low power laser diode (brand MicroPAD GI+). This study used the wavelength of 880nm, infrared, resonance mode, B frequency, power 100mW, dosage of 3 Joule for 60 seconds at the ST36 Zusanli, SP6 Sanyinjiao, ST40 Fenglong acupuncture points, and bilateral MA-IC3 ear acupuncture point. The laserpuncture therapy is done twice a week for 12 sessions (total of 6 weeks). *Sham* laserpuncture is done by putting the laser pen on the acupuncture points ST36 Zusanli, SP6 Sanyinjiao, ST40 Fenglong, and bilateral MA-IC3, but the laser device is not activated.

The outcomes measured in this study are VAS score, Interleukin 6 (IL-6) level, Interleukin 10 (IL-10) level, and nerve conduction velocity (NCV). Analysis of the outcome data is done using SPSS 23.0 program. The data was analyzed using paired *t*-test for the comparative hypotheses testing if the numeric variable of two paired group is having a normal distribution (for inter-group analysis). If the distribution is not normal, Wilcoxon test is used. Independent *t*-test is used for the comparative hypotheses testing if the numeric variable of two independent group is having normal distribution (for inter-group analysis). If the distribution is not normal, Mann-Whitney test is used. If a *p* value of $p < \alpha$ ($p < 0.05$) is obtained in the comparative hypotheses testing, then there is a significant difference between the compared variables. If the *p* value is $p > \alpha$ ($p > 0.05$), then there is no significant difference between the compared variables.

3. Results

3.1. Study subject characteristic

The descriptive test on the characteristics of the study subjects includes age, gender, level of education, length of having DM per year, HbA 1c level, DME score, DNS score, VAS score, drugs used, and insuline use. The result showed no significant difference, therefore the data can be analyzed for comparison.

3.2. Comparison of VAS score, IL-6 level, IL-10 level, and nerve conduction velocity between combined laserpuncture and pharmacological therapy group and *sham* laserpuncture and pharmacological therapy group.

Table 1. Comparison of VAS score between combined laserpuncture and pharmacological therapy group and *sham* laserpuncture and pharmacological therapy group

Mean \pm SD	Laserpuncture and pharmacological therapy group	<i>Sham</i> laserpuncture and pharmacological therapy group	<i>P</i>
Δ VAS score	-4.12 ± 1.204	-1.37 ± 0.718	0.000* ⁺

*Mann-Whitney

⁺Clinically significant difference

Table 1 showed the comparison of the *mean* value of Δ VAS score between the combined laserpuncture and pharmacological therapy group (-4.12) and *sham* laserpuncture and pharmacological therapy group (-1.37) which is statistically significant ($p < 0.001$).

Table 2. Comparison of IL-6 level and IL-10 level between combined laserpuncture and pharmacological therapy group and *sham* laserpuncture and pharmacological therapy group

Median (min-max)	Laserpuncture and pharmacological therapy group	<i>Sham</i> laserpuncture and pharmacological therapy group	<i>P</i>
IL-6	-0.12 (-2.04 - 17.66)	-0.395 (-17.28 - 5.33)	0.318*
IL-10	0.05 (-0.08 - 0.66)	-0.075 (-1.40 - 0.56)	0.032* ⁺

*Mann-Whitney

⁺Clinically significant difference

Table 2 showed the comparison of the *median* value of IL-6 level between the combined laserpuncture and pharmacological therapy group (-0.12) and *sham* laserpuncture and pharmacological therapy group (-0.395) which is not statistically significant ($p = 0.318$); and showed the comparison of the *median* value of IL-10 level between the combined laserpuncture and pharmacological therapy group (0.05) and *sham* laserpuncture and pharmacological therapy group (0.075) which is statistically significant ($p = 0.032$)

Table 3. Comparison of nerve conduction velocity between combined laserpuncture and pharmacological therapy group and *sham* laserpuncture and pharmacological therapy group

Median (min-max)	Laserpuncture and pharmacological therapy group	Sham laserpuncture and pharmacological therapy group	<i>P</i>
Right ankle peroneal motoric latency	0.000 (-4.8-13.8)	0.000 (-1.47-1.50)	0.724*
Left ankle peroneal motoric latency	0.000 (-1.57-4.8)	0.000 (-2.93-1.40)	0.926*
Right ankle peroneal motoric NCV	0.000 (-40.0-27.0)	0.000 (-4.20-10.3)	0.468*
Left ankle peroneal motoric NCV	- 0.15 (-12.0-31.0)	- 2.6 (-32.8-12.1)	0.196*
Right ankle peroneal motoric amplitude	0.000 (-2.00-1.47)	0.000 (-0.83-1.36)	0.867*
Left ankle peroneal motoric amplitude	0.000 (-0.65-1.43)	- 0.25 (-1.61-1.21)	0.100**
Right ankle tibialis motoric latency	- 0.67 (-5.50-1.60)	- 0.035 (-2.53-2.97)	0.082**
Left ankle tibialis motoric latency	- 0.120 (-3.53-1.50)	-0.065 (-2.23-1.50)	0.954**
Right ankle tibialis motoric NCV	- 0.45 (-35.0-5.4)	- 0.7 (-12.6-32.0)	0.926*
Left ankle tibialis motoric NCV	0.000 (-3.20-13.0)	- 2.35 (-14.5-8.30)	0.00* ⁺
Right ankle tibialis motoric amplitude	- 0.1440 (-10.32-3.55)	- 2.17 (-9.01-1.11)	0.527**

Table 3. (Continued)

Left ankle tibialis motoric amplitude	- 0.10 (- 2.72-2.54)	- 0.56 (-4.74-2.85)	0.132**
	.	.	.
Right ankle peroneal sensory latency	0.00 (-2.20-2.40)	0.00 (-2.63-3.80)	0.361*
	.	.	.
Left ankle peroneal sensory latency	0.00 (-2.02-2.80)	0.00 (-2.45-3.18)	0.780*
	.	.	.
Right ankle peroneal sensory NCV	0.00 (-2.90-77.30)	0.00 (-45.60-75.90)	0.616*
	.	.	.
Left ankle peroneal sensory NCV	0.00 (-13.0-87.30)	0.00 (-53.10-57.10)	0.642*
	.	.	.
Right ankle peroneal sensory amplitude	0.00 (3.86-11.00)	0.00 (-4.48-3.96)	0.540*
	.	.	.
Left ankle peroneal sensory amplitude	0.00 (-4.34-11.0)	0.00 (-5.73-3.67)	0.590*
	.	.	.
Right suralis sensory latency	0.00 (-1.32-2.45)	0.00 (-0.75-1.60)	0.956*
	.	.	.
Left suralis sensory latency	0.00 (-0.85-4.80)	0.00 (-4.20-2.75)	0.119*
	.	.	.
Right suralis sensory NCV	0.00 (-9.70-38.00)	0.00 (-11.70-6.70)	0.926*
	.	.	.
Left suralis sensory NCV	0.00 (-49.40-33.00)	0.00 (-54.50-43.60)	0.867*
	.	.	.
Right suralis sensory amplitude	0.00 (-2.63-7.42)	0.00 (-4.79-1.22)	0.780*
	.	.	.
Left suralis sensory amplitude	0.00 (-6.79-6.23)	0.00 (-6.68-3.59)	0.926*
	.	.	.

*Mann-Whitney

**Paired *t*-test

†Clinically significant difference

Table 3 showed the comparison of the *median* of NCV before and after treatment between combined laserpuncture and pharmacological therapy group and *sham* laserpuncture and pharmacological group. The difference is statistically significant in left ankle tibialis motoric NCV, while the rest is not significant ($p \leq 0.05$).

4. Discussion

DN is a series of processes that relied on many factors, therefore the treatment and prevention of it is basically a part of the management of DM as a whole. To prevent DN from developing into diabetic ulcers, such as foot ulcer or gangrene, a specialized effort is needed, with the hope of removing or at least reducing the symptoms, so that the patient's quality of life can be improved [1].

Laserpuncture is one of the modalities of acupuncture that uses low intensity laser that can cause nerve regeneration through the increase in nerve metabolism by increasing myelination and axonal regeneration, preventing motoric cell degeneration, and inducing the proliferation of schwann cells. During nerve recovery, the irradiation of 904nm low level laser therapy (LLLT) increased the number of wide diameter axons and increased the regeneration process of peripheral nerves. Low intensity laser light modulates inflammatory effects on injured tissues by altering the distribution of inflammatory cells, reducing edema and bleeding, and reducing necrosis. The reduction of edema will quicken the resolution of inflammatory processes [6]. The release of cytokines and growth factors into the circulation will cause a systemic vasodilatation and the formation of new capillaries.

Laserpuncture also reduces the prostaglandine concentration; promote the synthesis of ATP on pain receptors, which causes hyperpolarization, thus increasing the pain threshold by up to 50%; increasing the release opioid peptides (enkephaline, endorphine, and dynorphine); increasing cellular oxygen supply; and increasing the

proliferation of fibroblasts that can increase the forming of collagens and elastins [7].

Aside from the aforementioned treatment effects, the improvement of DN is affected by the blood sugar level, therefore a strict glycemic control is needed; by increasing insulin sensitivity and reducing insulin resistance. One of the mechanism of acupuncture is increasing the activity of cholinergic nerves and increasing NOS activity by reducing the concentration of plasma free fatty acid; these will improve glucose tolerance by increasing the regulation of insulin signalling proteins, thus facilitate insulin activity [8]. Acupuncture stimulation also causes serotonin secretion which will stimulate the secretion of β endorphine by the adrenal gland; β endorphine will stimulate the opioid receptors on peripheral muscles to increase glucose usage and reducing the plasma glucose level [9].

In this study, there is a statistically significant difference in the *mean* VAS score between the laserpuncture and pharmacological therapy group and *sham* laserpuncture and pharmacological therapy group ($p < 0.001$); a statistically significant increase in IL-10 level before and after treatment between the two groups ($p = 0.023$); a statistically significant improvement in left tibialis motoric NCV before and after treatment between the two groups ($p = 0.007$), in the laserpuncture and pharmacological therapy group 0.00 (- 3.20-13.00) and the *sham* laserpuncture and pharmacological therapy -2.35 (-14.5-8.30). Based on this results, the combination of laserpuncture and pharmacological therapy showed a good effect on the improvement of DN symptoms.

In this study, the IL-6 level is found to be statistically insignificant ($p = 0.318$). This can occur due to various inflammatory mediators such as TNF- α , IL-1, IL-6, and IL-8 which possessed roles in the pathogenesis of DM [10]; the pharmacological treatment of DM in general affects these mediators. In this study, all the subjects received pharmacological

therapy, therefore the inflammatory mediators, especially IL-6, can be reduced without the laserpuncture intervention. Besides, the general factors that caused the increase in IL-6 level are obesity, stress, lack of sleep, high sugar diet, smoking, and overtraining [11]. A stricter surveillance on the study subjects is required in order to prevent bias in the study results.

In this study, there are different results on the NCV. This can be caused by many physiological factors that can affect NCV: age, gender, height, weight, body mass index (BMI), and other non-physiological factors. Some technical factors that can affect the NCV value are skin surface temperature, hand position, and stimulation distance [12]. Other possible cause is that the length of this study is 6 weeks, while the time needed for the restoration of the peripheral nerve lesion is different depending on the process; the time needed is faster in segmental demyelination because there is no axonal damage; in axonal degeneration or Wallerian degeneration the time needed can be several months to a year, because the process of healing involves nerve regeneration continued by muscle, sensory organ, and blood vessel reinnervation, before a normal function is achieved [13]. Besides, the peroneal nerve comes from the distal part of ischiadicus nerve above the fossa poplitea, which gives innervation of both motoric and sensory, while the tibialis nerve comes from the distal ischiaducis nerve inside the fossa poplitea which gives mostly motoric innervation; therefore in this study there is an increase in NCV of the motoric tibialis nerve [13].

In this study, no side effects was found in the usage of laser therapy but there are complaints of pain and hematoma (2 subjects) during venous puncture to collect blood sample for the measurement of IL-10 level, and complaints of pain during the NCV measurement. It can be said that laserpuncture is proven to be safe if done according to the indication and observing the contraindication as described in the exclusion criteria of this study.

5. Conclusion

- Laserpuncture and pharmacological therapy showed some effects on patients with DN in the lower extremity.

- There is a statistically significant difference in the *mean* Δ VAS score before and after treatment between the combined laserpuncture and pharmacological therapy group (-4.12 ± 1.204) and the *sham* laserpuncture and pharmacological therapy group (-1.37 ± 0.718) with the *p* value < 0.001 .

- There is no statistically significant difference in the *mean* IL-6 level before and after treatment between the combined laserpuncture and pharmacological therapy group [-0.12 ($-2.04-17.66$)] and the *sham* laserpuncture and pharmacological therapy group [-0.395 ($-17.28-5.33$)] with the *p* value = 0.318.

- There is a statistically significant difference in the *mean* IL-10 level before and after treatment between the combined laserpuncture and pharmacological therapy group [0.05 ($-0.08-0.66$)] and the *sham* laserpuncture and pharmacological therapy group [-0.075 ($-1.40-0.56$)] with the *p* value = 0.032.

- There is a statistically significant difference in the *mean* left ankle tibialis motoric NCV before and after treatment between the combined laserpuncture and pharmacological therapy group [0.00 ($-3.20-13.0$)] and the *sham* laserpuncture and pharmacological therapy group [2.35 ($-14.50-8.30$)] with the *p* value = 0.007.

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