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Effect of electroacupuncture on symptoms of diabetic neuropathy (nerve damage that is caused by diabetes)

Submission date
30/08/2022

Recruitment status
No longer recruiting

Registration date
12/09/2022

Overall study status
Completed

Last Edited
03/07/2025

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Diabetic neuropathy is one of the most common chronic complications of diabetes; however, its diagnosis is difficult and late. As a result of this, there are few treatment options and the majority of them are focused on neuropathic symptoms with the risk of potential adverse effects, leading to treatment discontinuation.
Since its management has been unsuccessful, in 2014, the World Health Organization suggested the implementation of new therapies, such as electrostimulation, and most recently and less invasive, the use of acupuncture and electroacupuncture.
In the way that electroacupuncture is a variation of acupuncture where in addition to the insertion of the needle, an alternating frequency electric current is applied. There are currently some clinical trials on its efficacy and safety; however, the results are inconsistent as they are focused on subjective outcomes such as reduction of neuropathic symptoms, pain and improvement in quality of life. They also lack of strict ethical guidelines and more objective outcomes, which is why this clinical trial focuses not only on the clinical part, but also complements the electrophysiological, biochemical, molecular, inflammatory and genetic changes compared to a sham control group after 32 sessions of intervention.

Who can participate?
Patients with type 2 diabetes of 5 to 15 years of diagnosis, aged 40 to 75 years old, with clinical and electrophysiological diabetic peripheral polyneuropathy.

What does the study involve?
Eligible participants with a clinical and electrophysiological diagnosis of diabetic polyneuropathy will be randomly assigned either to a sham control group or an interventional electroacupuncture group, applied in a total of 32 sessions.
With the aim to evaluate the efficacy, effectiveness and safety of electroacupuncture as a possible concomitant treatment of neuropathic symptoms and disease progression by the clinical, electrophysiological, biochemical and molecular evaluation at baseline, after the first and second cycle of intervention, respectively, and three months after the end of the intervention.

What are the possible benefits and risks of participating?
Possible benefits:
-This study may provide clinical and scientific information for the approach to neuropathic pain in the affected or at-risk population.
-Patients will not receive any benefit of economic, physical, or preferential care in the treatment outside the research protocol.
-Patients will receive a full clinical evaluation, with the interpretation of the laboratory and cabinet studies, as well as medical attention at no cost.
-This study will give personalized attention to participants, which can guide them to a better diagnosis, treatment, and prevention of future diabetic complications.
-If patients present any alteration at the beginning or during the study derived from it, we will support them with the necessary medical attention.
Possible risks:
-The present study has a risk greater than the minimum supported by art. 17 and 17 bis of the General Health Law where the risks to health are evaluated, since during the study needles will be used for different procedures such as in the extraction of blood, in the study of nerve conduction velocity and in the application of electroacupuncture.
-A total of 12 ml (three tubes of 4 ml each) of blood sample for the determination of biochemical parameters will be obtained from the fold of one of the arms, this amount of blood will not pose any risks.
-For nerve conduction velocity study, electrodes are usually safe, although it is important to mention that frequencies with electrical voltage are used, and there may be risks such as mild pain at the site of placement.
-For electroacupuncture intervention, acupunctural points will be applied in different parts of the body with a duration of 20 minutes per session, with needles used during the study will be sterile, new, and disposable; the packaging will be shown before it is used, to verify that it meets these characteristics. The intervention does not involve a health risk, however, less common but more serious adverse events are burns, dermal injuries, syncope (dizziness), abscess, and rupture of the electroacupuncture needle.

Where is the study run from?
1. Medical Research Unit in Biochemistry, High Specialty Medical Unit "Dr. Bernardo Sepúlveda", National Medical Center Siglo XXI, IMSS, Mexico City.
2. IMSS Family Medicine Unit 41, Mexico City.
3. Escuela Nacional de Medicina y Homeopatía, IPN, Mexico City.

When is the study starting and how long is it expected to run for?
January 2020 to June 2025

Who is funding the study?
1. Fundación IMSS.
2. Medical and biological sciences master's degree department from the Superior School of Medicine (ESM) of the National Polytechnic Institute of Mexico.

Who is the main contact?
PhD José de Jesús Peralta Romero, attached to the Unidad de Investigación Médica en Bioquímica of the Unidad Médica de Alta Especialidad "Dr. Bernardo Sepúlveda", Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social.
drjjperalta@gmail.com, drjperalta@hotmail.com
Sub-investigators and Scientific Queries Contact Team
María Fernanda Pérez Hernández, MsC.

Sergio de Jesús Aguilar Castillo, MD.
Alejandra Calderón Vallejo. MsC.
Cuauhtémoc Daniel Gómez Jiménez, MsC.
Eduardo Rodríguez Guerrero, MsC.
Mónica Luz Gómez Esquivel, PhD.
Juan Manuel Ordóñez Rodríguez, MsC.
Macedonia Guadalupe Moreno Tovar, MD.
Fátima Aguilar Morales, MD.
María Esther Ocharan Hernández, PhD.
Claudia Camelia Calzada Mendoza, PhD.
Mónica Ascención De Nova Ocampo, PhD.
Germán Velázquez García, MsC.
Citlaltepetl Salinas Lara, PhD.
Laura Ávila Jiménez, PhD.
Miguel Cruz López, PhD.
Generic email address for scientific queries research team members: protocolo.nd.ea@gmail.com

Contact information

Type(s)
Public, Principal Investigator

Contact name
Dr José de Jesús Peralta Romero

ORCID ID
https://orcid.org/0000-0001-5426-5555

Contact details
Av. Cuauhtémoc 330 Colonia Doctores
Delegation Cuauhtémoc
Mexico City
Mexico
06720
+52 55 3231 8563
drjjperalta@gmail.com

Type(s)
Scientific

Contact name
Dr María Fernanda Pérez Hernández

ORCID ID
https://orcid.org/0000-0002-2141-7804

Contact details
Av. Cuauhtémoc 330 Colonia Doctores
Delegation Cuauhtémoc
Mexico City

Mexico
06720
+52 55 74 02 10 93
marferperezh@gmail.com

Type(s)
Public, Principal Investigator

Contact name
Dr José de Jesús Peralta Romero

Contact details
Av. Cuauhtémoc 330 Colonia Doctores
Delegation Cuauhtémoc
Mexico City
Mexico
06720
+52 55 3231 8563
drjperalta@hotmail.com

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
NCT05521737

Secondary identifying numbers
2020-785-070

Study information

Scientific Title
Effect of electroacupuncture on sensitive symptoms of distal diabetic peripheral neuropathy and its correlation with nerve conduction changes

Acronym
EA&DPN

Study objectives
Electroacupuncture reduces diabetic neuropathy symptoms ans improves nerve conduction velocity of sural nerve more than sham acupuncture.

Ethics approval required
Old ethics approval format

Ethics approval(s)

1. Approved 22/05/2020, Comisión Nacional de Bioética (Av. Marina Nacional 60-piso 15, Tacuba, Miguel Hidalgo, C.P. 11410 CDMX Ciudad de México, CDMX, Mexico; +52 55 5487 2760; chb.conbioetica@salud.gob.mx), ref: R-2020-785-070
2. Approved 18/11/2022, CONBIOÉTICA (Calzada Arenal No. 134 esq. Xochimaltzin, Col. Arenal Tepepan, Tlalpan, Mexico City, 14610, Mexico; (55)54872760; conbioetica.contacto@salud.gob.mx), ref: CONBIOÉTICA-09-CEI-009-20160601
Approved by Comisión Nacional de Bioética in 26th May 2020 and reapproved in 18th November 2022.

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital, Laboratory, Telephone, University/medical school/dental school

Study type(s)
Diagnostic, Prevention, Quality of life, Screening, Treatment, Safety, Efficacy

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Effect of electroacupuncture on symptoms and nerve conduction velocity for coadjuvant treatment of diabetic peripheral neuropathy.

Interventions
Current interventions as of 23/08/2023:

Controlled clinical trial to evaluate the effect of electroacupuncture on the reduction of neuropathic pain, quality of life, changes in sensory, motor nerve conduction velocity, oxidative stress, inflammatory response, and genetic expression in patients with type 2 diabetes mellitus and diabetic polyneuropathy, beneficiaries of the Mexican Social Security Institute, from the family medical centres 20, 40 and 41 at north of CDMX.

SCREENING
Initially, a brief questionnaire will be carried out by telephone to identify possible candidates who meet the inclusion criteria for the study, after which they will be summoned to their corresponding family medicine unit for examination.
Once their participation in the study has been accepted by informed consent signature, a physical examination will be performed by a general practitioner, focused on the clinical diagnosis of diabetic polyneuropathy. The MNSI, MDNS, DN-4 and NRS questionnaires will be applied, in addition to the SF-36 for quality of life.
Subsequently, a specialist neurologist will corroborate the physical examination and the clinical diagnosis of diabetic polyneuropathy in order to screen the patient by means of a nerve

conduction velocity study performed by a neurophysiologist in order to obtain the electrophysiological diagnosis.
Only people with a diagnosis of symmetric distal polyneuropathy will continue to receive treatment, and patients will be allocated into two different interventional groups by simple randomization using an online software.
Previously to the intervention, enrolled participants will be assigned an appointment for laboratory studies that will be taken after fasting for 8 to 10 hours, to determine serum levels of glucose, urea, creatinine, uric acid, triglycerides, total cholesterol, HDL and LDL.

INTERVENTION.
Interventional groups:

Control / Sham group: Sham Acupuncture.
Intervention consists of a total of 32 sessions, divided into two intervention cycles, that is, 16 sessions over 2 months, with a rest period of 1 month in between. Sham acupuncture is applied using a non-puncture device without electrical stimulation at the same acupunctural points as in the electroacupuncture group

Interventional group: Electroacupuncture.
Intervention consists of a total of 32 sessions, divided into two intervention cycles, that is, 16 sessions over 2 months, with a rest period of 1 month in between. EA is applied for 20 minutes at an alternating frequency of 2 Hz. Acupunctural points are Zusanli (E36), Fenlong (E40), Yinlingquan (B9), Sanyinjiao (B6), Taichong (H3) and Zulinqi (VB41).

EFFICACY AND SAFETY
At the end of both cycles of intervention and three months without receiving acupuncture, the questionnaires, the nerve conduction velocity study, and the biochemical and molecular studies will be re-evaluated to analyse the changes throughout the study and the efficacy of electroacupuncture compared to the control group.
Throughout the study, participants will be followed up weekly by telephone to identify possible adverse effects of the intervention.

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Previous interventions:

A controlled clinical trial to evaluate the effect of electroacupuncture on the reduction of neuropathic pain, quality of life and changes in sensory and motor nerve conduction velocity in patients with type 2 diabetes mellitus, beneficiaries of the Mexican Social Security Institute, from the family medical centers 20, 40 and 41 at north of CDMX.

Patients will receive acupuncture intervention for two months.
Participants will be randomised by the stratification of diabetic neuropathy scale of severity, using the online software OxMaR 2014, or the Oxford Minimization and Randomization program.

Sham group: Sham Acupuncture.
Sham acupuncture will be administered in a total of 16 sessions of 20 minutes each one, for 2 months.

Interventional group: Electroacupuncture.
Electroacupuncture will be administered in a total of 16 sessions of 20 minutes each one, for 2 months.

Once the acceptance letter has been signed, a series of questionnaires and a physical examination will be carried out to meet the necessary criteria to continue participating.

Exclusively the doctor who carried out the previous evaluation will determine if candidates can continue with participation. If so, laboratory studies will be taken after fasting for 8 to 10 hours, to determine serum levels of glucose, urea, creatinine, uric acid, triglycerides, total cholesterol, HDL and LDL.

Enrolled participants will be assigned an appointment to be evaluated by a neurologist and undergo a nerve conduction velocity study by a neurophysiologist.

Only people with a diagnosis of symmetric distal polyneuropathy will continue to receive the acupuncture intervention for two months, 16 sessions in total, two sessions per week.

At the end of the intervention, the questionnaires, the biochemical studies, and the nerve conduction velocity study will be applied again.

Finally, to evaluate the intervention over time, patients will be called three months after the intervention ends, with the intention of re-evaluating the questionnaires, the biochemical studies, and the nerve conduction velocity study.

Intervention Type
Procedure/Surgery

Primary outcome measure
Current primary outcome measure as of 23/08/2023:

Nerve Conduction Velocity
Measured by Nerve Conduction Velocity Study using the VIKING LIFE-SAVING EQUIPMENT with a baseline evaluation, after the first and second cycle of intervention, respectively, and three months after the end of the intervention, to determine Motor and Sensitive Nerve Conduction Velocity of the common peroneal nerve, sural nerve, and tibial nerve. Sensitive Nerve Conduction (SCV). The distance between the receiving point and the stimulus point. SCV normal values: Peroneal nerve ≥ 41 m/s, tibial nerve ≥ 44 m/s, sural nerve ≥ 50 m/s. Motor Conduction Velocity (MCV).
The distance between two points and the difference in incubation between them after superstimulation of the corresponding nerve branch. MCV normal values: Peroneal nerve ≥ 41 m /s, tibial nerve ≥ 44 m/s, sural nerve ≥ 60 m/s. *Values below those stipulated above indicate that NCV has slowed down and is abnormal. The investigators expect a diminishment of SCV and MCV in the sham acupuncture group from the first cycle of intervention, whereas the electroacupuncture group remains unchanged or even increases SCV and MCV.

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Previous primary outcome measure:

1. Location, duration and severity of clinical signs and symptoms of diabetic peripheral neuropathy measured using the Michigan Neuropathy Screening Instrument (MNSI) sensitive symptoms scale at 2 months
2. Foot condition measured using Michigan Neuropathy Screening Instrument (MNSI) clinical Inspection at 2 months

3. Michigan Neuropathy Screening Instrument (MNSI). Vibratory sensation at 2 months
4. Michigan Neuropathy Screening Instrument (MNSI). Ankle reflexes at 2 months
5. Pressure sensation measured using Semmes-Weinstein monofilament (10 g monofilament test) at 2 months
6. Cranial nerves, muscle weakness, reflexes, and sensation of upper and lower limbs measured using the Neuropathy Deficit Score (NDS) at 2 months

Secondary outcome measures

Current secondary outcome measures as of 23/08/2023:

1. Michigan Neuropathy Screening Instrument (MNSI).
It will be assessed with a lower extremity examination by a health professional of both feet in search of deformities, dry skin, calluses, infections, fissures and ulcers. Complemented with measurement of vibratory sensation, ankle reflexes, and Semmes-Weinstein monofilament test at baseline, after the first and second cycle of intervention, respectively, and three months after the end of the intervention. The investigators expect improvement in the physical aspect of the foot in the electroacupuncture group, while in the sham acupuncture group, the complication progresses.
2. Michigan Diabetic Neuropathy Score (MDNS)
Composed of three items where the sensory compromise is evaluated at baseline, after the first and second cycle of intervention, respectively, and three months after the end of the intervention, with the perception of vibration, 10 gr. monofilament and pin prick, in addition to the muscular strength of the toes, and the bicipital, tricipital, quadriceps and achilles muscle reflexes. The investigators expect a diminishment of the MDNS score and clinical improvement in the electroacupuncture group and progression of clinical manifestations in the sham group.
3. Douleur Neuropathique en 4 Questions (DN-4)
A screening tool for neuropathic pain consisting of 10 interview questions (DN4-interview) and physical tests evaluated at baseline, after the first and second cycle of intervention, respectively, and 3 months after the end of the intervention. A score greater than 4 points suggests neuropathic pain. The investigators expect decreased scores in the electroacupuncture group and increased or persistent scores in the sham group.
4. Numerical Pain Rating Scale (NRS)
Patients are only asked at baseline, after the first and second cycle of intervention, respectively, and three months after the end of the intervention, to circle the number between 0 and 10, 0 and 20 or 0 and 100 that best matches the intensity of their pain currently and in the last 7 days, where zero usually represents "no pain", while the upper limit represents "the worst pain of their life". The investigators expect a diminishment of the rating scale in the electroacupuncture group and an increase in the sham acupuncture group.
5. Quality of life (SF-36)
It will be measured at baseline, after the first and second cycle of intervention, respectively, and three months after the end of the intervention by The Short Form-36 Health Survey (SF-36) a measure of health status that consists of eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social functioning, and mental health), which are the weighted sums of the questions in their section. The investigators expect quality of life improvement in the electroacupuncture group, while in the sham acupuncture group it might worsen.
6. Oxidative Stress [Time Frame: Baseline evaluation, after the first and second cycle of intervention, respectively, and three months after the end of the intervention]
Determined at baseline, after the first and second cycle of intervention, respectively, and three months after the end of the intervention by quantifying the concentrations of the lipoperoxidation product Malondialdehyde (MDA). An increase of MDA is expected in the sham

group, while in the electroacupuncture group it is expected to decrease.
7. Inflammatory response.
Assessed at baseline, after the first and second cycle of intervention, respectively, and three months after the end of the intervention by changes in serum concentrations of proinflammatory (IL-6, IL1β, TNF-α and IL-18) and anti-inflammatory (IL-10) cytokines determined by quantitative ELISA by flow cytometry. The investigators expect an increase in anti-inflammatory cytokines and a decrease in proinflammatory cytokines in the electroacupuncture group, while in the sham group, this is inversely presented.
8. Genetic expression
mRNA expression at baseline, after the first and second cycle of intervention, respectively, and three months after the end of the intervention, of 5-HT1AR, Neurokinin 1, α-adrenoreceptors, NGF (Nerve growth factor), CX3CR1, GAP-43 (Growth associated protein 43) and Neurotrophin (NT3), (Chemoline receptor 1) genes quantified by real-time PCR. The investigators expect an increase in gene expression in patients with electroacupuncture, while in sham patients it is decreased or even unchanged.

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Previous secondary outcome measures:

1. Nerve Conduction Velocity. Measured by electromyogram (EMG), carried out by an EMG specialist to ensure the accuracy of EMG reading at 2 months
2. Sensory Testing Nerve Conduction (SCV). Determined using the reverse method, with a proximal stimulus and remote reception at 2 months
3. Motor Conduction Velocity (MCV) measured using electromyography at 2 months
4. Quality of life measured by The Short Form-36 Health Survey (SF-36) at 2 months

Overall study start date
01/01/2020

Completion date
10/06/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 23/08/2023:

1. Patients with type 2 diabetes
2. Patients with clinical diabetic peripheral polyneuropathy
3. Patients with electrophysiological diagnosis of diabetic peripheral polyneuropathy in its different types of classification

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Previous inclusion criteria:

Patients with type 2 diabetes of 5 to 15 years of diagnosis, 40 to 60 years old, with clinical and electrophysiologic diabetic peripheral polyneuropathy, neuropathic pain.

Participant type(s)

Patient

Age group
Adult

Lower age limit
40 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
The total sample size of 50 participants, divided into two different interventional groups. Sham control group of 25 participants and Electroacupuncture experimental group of 25 participants.

Total final enrolment
40

Key exclusion criteria
Current exclusion criteria as of 23/08/2023:

1. Type 1 diabetes or gestational diabetes
2. Systemic autoimmune diseases
3. Hematological disorders
4. HIV diagnosis
5. Cancer in treatment
6. Pregnancy
7. Other types of neurological disorders or neuropathies
8. History of spine or hip trauma
9. Intervention with acupuncture 6 months previously
10. Patients with pacemakers

Previous exclusion criteria:

Patients with systemic autoimmune diseases, hematological disorders, HIV, cancer history, pregnancy, intervention with acupuncture 6 months before.

Date of first enrolment
01/11/2021

Date of final enrolment
21/01/2025

Locations

Countries of recruitment
Mexico

Study participating centre
Centro Médico Nacional Siglo XXI, IMSS
Av. Cuauhtémoc 330
Colonia Doctores
Delegation Cuauhtémoc
Mexico City
Mexico
06720

Study participating centre
Escuela Nacional de Medicina y Homeopatía, IPN.
Av. Guillermo Massieu Helguera 239, La Purísima Ticoman, Gustavo A. Madero.
Mexico City
Mexico
07320

Study participating centre
Escuela Superior de Medicina, IPN
Salvador Díaz Mirón, Casco de Santo Tomas, Miguel Hidalgo
Mexico City
Mexico
11340

Study participating centre
Facultad de Estudios Superiores Iztacala, UNAM
Av. de los Barrios 1, Hab Los Reyes Ixtacala Barrio de los Árboles/Barrio de los Héroes, Tlalnepantla de Baz.
State of Mexico
Mexico
54090

Study participating centre
Facultad de Estudios Superiores Zaragoza, UNAM.
Av Guelatao 66, Ejército de Oriente, Ignacio Zaragoza
Mexico City
Mexico
09230

Study participating centre
Universidad Intercultural del Estado de México Plantel Tepetlixpa
Av. 20 de Noviembre, La Ermita, Tepetlixpa
State of Mexico
Mexico
56880

Study participating centre
IMSS Family Medicine Unit 41
Av Fortuna 344, Magdalena de las Salinas, Gustavo A. Madero
Mexico City
Mexico
07760

Study participating centre
Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez
Insurgentes Sur 3877, La Fama, Tlalpan
Mexico City
Mexico
14269

Sponsor information

Organisation
Instituto Mexicano del Seguro Social

Sponsor details
Av. Marina Nacional 60-piso 15
Tacuba
Miguel Hidalgo
Mexico City
Mexico
11410
+52 55 5487 2760
chb.conbioetica@salud.gob.mx

Sponsor type
Research organisation

Funder(s)

Funder type
Government

Funder Name
Coordinación de Investigación en Salud. Instituto Mexicano del Seguro Social

Results and Publications

Publication and dissemination plan
Planned publication in a high-imppact peer-reviewed journal.

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
The datasets generated and analysed during the current study will be available upon request from the principal investigator, PhD José de Jesús Peralta Romero. Researcher attached to the Medical Research Unit in Biochemistry, High Specialty Medical Unit "Dr. Bernardo Sepúlveda", National Medical Center Siglo XXI, IMSS, Mexico City. E-mail: drjjperalta@gmail.com, drjperalta@hotmail.com

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet		22/08/2022	02/09/2022	No	Yes
Protocol file		26/08/2022	02/09/2022	No	No
Statistical Analysis Plan		24/08/2022	02/09/2022	No	No
Protocol article		15/02/2024	16/02/2024	Yes	No