

To explore the treatment of optic
neuromyelitis with
electroacupuncture(**NMOSD**)The efficacy and
mechanism of pain in patients

Project Source: Postgraduate Project

Research Unit: Guangdong Provincial Hospital of
Traditional Chinese Medicine

Head of Research: Zhao Yuanqi, Li Xiaojun

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1. Program summary

Research topic:	To explore the treatment of optic neuromyelitis spectrum disease by electroacupuncture (NMOSD) Study on the efficacy and mechanism of pain in patients
Purpose of the research	Main purpose: to observe the electrical target NMOSD Secondary purpose of the curative effect of patient pain: Discussion NMOSD The mechanism of pain in patients and the mechanism of electroacupuncture in the treatment of pain in patients with optic neuromyelitis spectrum disease
Research hypothesis	Electroacupuncture can be treated effectively. NMOSD Pain in the patient
Research design	Randomized controlled trial
Test group	Electroneedle group
Control group	False needle group
Sample size	20
Selection Criteria	1 Accord with 2021 Diagnostic criteria for optic poliomyelitis genealogical diseases in China's Guidelines for the Diagnosis and Treatment of optic Neurospinal Myelitis Gene Diseases; 2 NRS \geq 4 Score; 3 Patients use stable doses of biotherapy and/or strong loose, before joining the group 30 There is no adjustment plan within the day; 4 Patients before joining the group 30 No standard drug combinations for pain treatment, including antiepileptic drugs, antidepressants or opioids, were adjusted within the day. 5 The patient or the patient's family sign informed consent. 6 18-80 Year-year-old patient.
Exclusion criteria	1 <u>Patients participating in other clinical studies;</u> 2 Patients with low cognitive or mental ability; 3 People who are pregnant, breastfeed or plan to get pregnant during the study; 4 People with serious diseases related to the heart, liver, kidneys or hematopoietic system; 5 <u>Patients with diabetic peripheral neuropathy.</u>
Test cycle	Total test cycle 30 God, all 18 Visit twice a week.
Outcome evaluation indicators	Main indicators: NRS Mark

	Secondary indicators:EDSS、MPQ Rating, SAS Anxiety Scale, SDS Depression Scale, SF-36 Quality of life scale, IL6、TNF-A、fMRI Target
Safety evaluation indicators	Adverse reactions, blood routine, biochemistry, liver function

2. Research background

The pain is NMOSD A common symptom of the patient. Known as high as 86%Taxi NMOSD Patients will be affected by pain. [3,13,14,15]. A survey on the quality of life and medical experience of Chinese patients shows that pain is the third concern of patients in addition to recurrence and drug side effects, and even more trouble the lives of patients than disability. Weigh 10%The patient believes that the severe pain caused by the disease greatly interferes with normal life. 6%Patients believe that physical pain seriously prevents them from enjoying life.

NMOSD The pain of patients is mainly divided into neuropathological pain and spasm-related pain. Some clinical observations suggest clinical factors.(Such as poliomyelitis and emotions)And demographic factors(Such as age)Give NMOSD Pain-relatedness of patients[3,4,10,11]. At present NMOSD Possible mechanism of pain[32-36] : 1In the physiological state, AQP4 With excitatory amino acid transporter 2 (EAAT2) Common expression, so that astrocytes consume glutamate. AQP4-ab Positive patient's AQP4 In the absence, the intake of glutamate by astrocytes leads to the excessive accumulation of glutamate in the extracellular space, resulting in abnormal excitation of neurons and excitatory tissue damage.2The central nervous system regulates pain mainly from 2 Aspects: Increased excitement and reduction of inhibition. This 2 Each aspect is affected by reactive astrocyte proliferation and its related inflammatory reactions.3Abnormal brain structure: Studies found that the posterior ventral nucleus(VPN) Volume is negatively correlated with a variety of pain intensity indicators. The volume of hippocampus and pale bules in patients with neurological pain is smaller than that of patients with non-nervous pain, and the pain intensity is negatively correlated with the nucleus and thalamus volume.

At present, despite a variety of analgesic drugs and a variety of drug combinations for different pain mechanisms. [12], but there are still 60-80%Taxi NMOSD Patients with moderate and severe pain and completely get rid of pain are less than 10% [3,4]. At the same time, there are many large samples and multiple centers. RCT Research suggests that electroacupuncture is effective in treating pain. [25,26,41,42]. National Institutes of Health(National Institutes Of Health)Estimated, more than 1500 Ten thousand Americans use it.Acupuncture

therapy[27, 28]. The use of electric needles is now recognized by the World Health Organization.[29-31]. The author expounds the analgesic effect of electroacupuncture from the aspects of traditional Chinese medicine and modern medicine. Among them, the design of fake acupuncture is mainly published in BMC Acupuncture study of the same type of disease with pain in the journal[47].

Based on the results of the literature, some progress has been made in the study of electroacupuncture in the treatment of pain, which can be used to regulate inflammatory factors. [16,17,21-23], release analgesic-related factors[19,20,37,39-41], regulate the corresponding brain area[45,46]Activities and other aspects play an analgesic effect.

Therefore, this study hopes to explore the efficacy and related mechanism of electroacupuncture in the treatment of pain in patients with optic poliomyelitis spectrum diseases by comparing the efficacy of electroacupuncture group and the pseudo-acupuncture group. This study assumes that electricity has an effect on pain in patients with optic neuromyelitis spectrum disease, and then verifies the mechanism of electricity on the pain of patients with optic neuromyelitis genealogy diseases for clinical treatment options.

References:

- [1] Weinshenker B G, Wingerchuk D M. Neuromyelitis Spectrum Disorders[J]. Mayo Clinic Proceedings, 2017,92(4):663-679.
- [2] Kleiter I, Gahlen A, Borisow N, et al. Neuromyelitis optica: Evaluation of 871 attacks and 1,153 treatment courses [J]. Ann Neurol, 2016,79(2):206-216.
- [3] Qian P, Lancia S, Alvarez E, et al. Association of Neuromyelitis Optica With Severe and Intractable Pain [J]. Archives of Neurology, 2012,69 (11): 1482.
- [4] Ayzenberg I, Richter D, Henke E, et al. Pain, Depression, and Quality of Life in Neuromyelitis Optica Spectrum Disorder A Cross-Sectional Study of 166 AQP4 Antibody-Seropositive Patients [J]. NEUROLOGY-NEUROIMMUNOLOGY & NEUROINFLAMMATION, 2021,8(3).
- [5] Mealy M A, Boscoe A, Caro J, et al. Assessment of Patients with Neuromyelitis Optica Spectrum Disorder Using the EQ-5D [J]. Int J MS Care, 2019, 21(3): 129-134.
- [6] Beekman J, KEisler A, Pedraza O, et al. Neuromyelitis optica spectrum disorder: Patient experience and quality of life [J]. Neurol Neuroimmunol Neuroinflamm, 2019,6(4):e580.
- [7] Huang W, Zhang Bao J, Chang X, et al. Neuromyelitis optica spectrum disorder in China: Quality Of life and medical care experience [J]. Mult Scler Relat Disord, 2020, 46:102542.
- [8] Barzegar M, Sadeghi Bahmani D, Mirmosayyeb O, et al. Higher Disease and Pain Severity and Fatigue and Lower Balance Skills Are Associated with Higher Prevalence of Falling among Individuals with the Inflammatory Disease of Neuromyelitis Optica Spectrum Disorder (NMOSD) [J]. Journal of Clinical Medicine, 2020,9(11):3604.
- [9] Asseger S, Schmidt F, Chien C, et al. Pain in AQP4-IgG-positive and MOG-IgG-positive neuromyelitis optica spectrum disorders[J]. Multiple Sclerosis Journal - Experimental, Translational and Clinical, 2018,4(3):1043168524.
- [10] Tackley G, Vecchio D, Hamid S, et al. Chronic neuropathic pain severity is determined by lesion level in aquaporin 4-antibody-positive myelitis[J]. J Neurol Neurosurg Psychiatry, 2017,88(2):165-169.
- [11] Zhao S, Mutch K, Elson L, et al. Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life [J]. Mult Scler, 2014,20(12): 1658-1661.

- [12] Szok D, Tajti J, Nyári A, Vécsei L. Therapeutic Approaches for Peripheral and Central Neuropathic Pain. *Behav Neurol*. 2019;2019:8685954. Published 2019 Nov 21.
- [13] Kanamori, Y., Nakashima, I., Takai, Y., et al. (2011). Pain in neuromyelitis optica and its effect on quality of life: A cross-sectional study. *Neurology*, 77(7), 652–658.
- [14] Kim, H.J., Paul, F., Lana-Peixoto, et al. (2015). MRI characteristics of neuromyelitis optica spectrum disorder: An international update. *Neurology*, 84(11), 1165–1173.
- [15] Muto, M., Mori, M., Sato, et al. (2015). Current symptomatology in multiple sclerosis and neuromyelitis optica. *European Journal of Neurology*, 22(2), 299–304.
- [16] Chen Ruixiang. NLRP3 Inflammatory body pathway participation in spinal cord central mechanism and electroacupuncture intervention of rats with complex area pain syndrome[D]. Zhejiang Chinese Medical University, 2021.
- [17] Wang Zhifu. Study on the role and mechanism of spinal lipoxylin in neuropathological pain and electroacupuncture analgesia in rats[D]. Fudan University, 2013.
- [18] Lu Dahao. SIRT1/NLRP3 Study on the role and mechanism of signaling pathways in electroacupuncture in the treatment of central pain after stroke [D]. Yangzhou University, 2021.
- [19] Zhang Jing. Electricity against inflammation in local skin tissue of rat lesion with sexual pain: CB2 Influence of receptor protein expression[D]. Huazhong University of Science and Technology, 2009.
- [20] Zhou Xiaoxin. Study on the role and mechanism of electroacupuncture in neuropathological pain and postoperative cognitive dysfunction[D]. Shanghai Jiao Tong University, 2020.
- [21] Shen Wei. Analgesic mechanism of electroacupuncture in rat model of acute inflammatory pain: in the dorsal angle of the spinal cord p-ERK1/2, p-CREB, NPY and its influence on the expression of their receptors[D]. Lanzhou University, 2020.
- [22] Luo Huiying. Electroacupuncture stimulation is reduced by lowering glucocorticoid receptor Nav1.7 Study on the mechanism of expression to relieve inflammatory pain in rats[D]. Guangzhou University of Traditional Chinese Medicine, 2019.
- [23] Xiang Li. Wnt/B-Catenin Study on the role of signaling pathways in electroacupuncture in the treatment of neuropathological pain and its mechanism[D]. Southwest Medical University, 2019.
- [24] Han Jisheng. Design and application of Chinese acupuncture. 1994 Year 12 Moon 30 Day, 358-362 Page.
- [25] Heo I, Shin BC, Cho JH, et al. Multicentre randomised Controlled clinical trial of electroacupuncture with usual care for patients with non-acute pain after back surgery. *Br J Anaesth*. 2021 Mar;126(3):692-699.
- [26] Teoh AYB, Chong CCN, Leung WW, et al. Electroacupuncture-reduced sedative and analgesic requirements for diagnostic EUS: a prospective, randomized, double-blinded, sham-controlled study. *Gastrointest Endosc*. 2018;87(2):476-485.

- [27] Zhang Y, et al. Acupuncture Use among American Adults: What Acupuncture Practitioners Can Learn from National Health Interview Survey 2007 Evidence-based Complementary and Alternative Medicine: eCAM. 2012; 2012: 710750.
- [28] Clarke TC, et al. Trends in the use of complementary health approaches among adults: United States, 2002–2012. *Natl Health Stat Report*. 2015; (79):1–16.
- [29] Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007; 147(7):478–91.
- [30] Kong J, et al. Are all placebo effects equal? Placebo pills, Sham acupuncture, cue conditioning and their association. *PLoS One*. 2013; 8(7):e67485.
- [31] Eskinazi DP, Jobst KA. National Institutes of Health Office of Alternative Medicine-Food and Drug Administration Workshop on Acupuncture. *J Altern Complement Med*. 1996; 2(1):3–6.
- [32] Ji R, Donnelly C R, Nedergaard M. Astrocytes in chronic pain and itch[J]. *Nature reviews. Neuroscience*, 2019,20(11):667-685.
- [33] Hinson SR, Roemer SF, Lucchinetti CF, et al. Aquaporin-4-binding autoantibodies in patients with neuromyelitis optica impair glutamate transport by down-regulating EAAT2. *J Exp Med*. 2008;205(11): 2473-2481.
- [34] Bradl M, Kanamori Y, Nakashima I, et al. Pain in neuromyelitis optica--prevalence, pathogenesis and therapy[J]. *Nature reviews. Neurology*, 2014,10(9):529-536.
- [35] Asseyer S, Kuchling J, Gaetano L, et al. Ventral posterior nucleus volume is associated with Neuropathic pain intensity in neuromyelitis optica spectrum disorders[J]. *Mult Scler Relat Disord*, 2020, 46:102579.
- [36] Wang T, Lian Z, Wu X, et al. Subcortical structural abnormalities in female neuromyelitis optica patients with neuropathic pain [J]. *Mult Scler Relat Disord*, 2020, 37:101432.
- [37] Meng X, Zhang Y, Li A, et al. The effects of opioid receptor antagonists on electroacupuncture produced anti-allodynia/hyperalgesia in rats with paclitaxel-evoked peripheral neuropathy. *Brain Res* 2011; 1414:58–65.
- [38] Shimoyama M, Toyama S, Tagaito Y, Shimoyama N: Endogenous endomorphin-2 contributes to spinal-opioid antinociception. *Pharmacology* 2012; 89:145–8.
- [39] Léonard G, Cloutier C, Marchand S. Reduced analgesic effect of acupuncture-like TENS but not conventional TENS in opioid-treated patients. *J Pain*. 2011 Feb; 12(2):213-21.
- [40] Guo Yi. *Experimental acupuncture. China Traditional Chinese Medicine Press*. 2008. 175-181
- [41] Li Jiawen. Central neurotransmitter basis for acupuncture and analgesia. *Journal of Practical Chinese Medicine*. 2013, 27(1):160-163.
- [42] White P, Lewith G, Prescott P, et al. Acupuncture versus placebo for the treatment of chronic mechanical neck pain: a randomized, controlled trial. *Ann Intern Med*. 2004 Dec 21; 141(12):911-9.
- [42] Tu JF, Yang JW, Shi GX, et al. Efficacy of Intensive Acupuncture Versus Sham Acupuncture in Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Rheumatol*. 2021 Mar; 73(3):448-458.

- [43] Kong JT, Puetz C, Tian L, et al. Effect of Electroacupuncture vs Sham Treatment on Change in Pain Severity Among Adults With Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA Netw Open*. 2020 Oct 1;3(10):e2022787.
- [44] Lin JG, Lo MW, Wen YR, et al. The effect of high and low frequency electroacupuncture in pain after lower abdominal surgery. *Pain*. 2002 Oct;99(3):509-514.
- [45] Treede RD. Transduction and transmission properties of primary nociceptive afferents. *Ros Fiziol ZhIm IM Sechenova* 1999,85(1):205-211.
- [46] Shi Yu, Wu Wen's Functional Magnetic Resonance Research Systematic Evaluation of the Mechanism of Acupuncture Analgesia *Chinese Journal of Basic Medicine of Traditional Chinese Medicine* 2018 Year, No. 24 Volume 11A whole year or month.
- [47] Quispe-Cabanillas JG, Damasceno A, von Glehn F, et al. Impact of Electroacupuncture on quality of life for patients with Relapsing-Remitting Multiple Sclerosis under treatment with immunomodulators: a randomized study. *BMC Complement Altern Med*. 2012 Nov 5; 12:209.

3. Objective: To observe the effect of electricity on pain in patients with optic neuromyelitis spectrum disease.

Secondary Purpose: Discuss NMOSD The mechanism of pain in patients and the mechanism of electroacupuncture in the treatment of pain in patients with optic neuromyelitis spectrum disease

4. Test design

Randomized controlled study

5. Case selection

5.1 Selection Criteria

1 Accord with 2021 Diagnostic criteria for optic poliomyelitis genealogical diseases in China's Guidelines for the Diagnosis and Treatment of optic Neurospinal Myelitis Gene Diseases;

2 NRS \geq 4 Score;

3 Patients use stable doses of biotherapy and/or strong loose, before joining the group 30 There is no adjustment plan within the day;

4 Patients before joining the group 30 No standard drug combinations for pain treatment, including antiepileptic drugs, antidepressants or opioids, were adjusted within the day.

5 The patient or the patient's family sign informed consent.

6 18-80 Year-year-old patient.

5.2 Exclusion criteria:

1 Patients participating in other clinical studies;

2 Patients with low cognitive or mental ability.

3 People who are pregnant, breastfeed or plan to get pregnant during the study;

4 People with serious diseases related to the heart, liver, kidney or hematopoietic system.

5 Patients with diabetic peripheral neuropathy.

5.3 Exclusion criteria:

Incorrectly included in the case;

Subjects took drugs that affected the relevant indicators of this study without authorization;

5.4 Fall off standard:

The subjects failed to complete the treatment as required by the researchers;

The subjects did not cooperate with the arrangement for personal reasons, and the researchers believed that the patient had poor compliance and was not suitable for research;

The subjects withdrew from the study on their own.

6. Sampling estimation and grouping method

6.1 Estimate of sample size

The spectrum disease of optic neuromyelitis is a rare disease, and this study is an exploratory study. Referring to previous studies, the sample size of this topic is 20 Example.

6.2 Random grouping method

Use a simple randomization method to input the estimated sample content. SPSS V.25.0 Statistical software to obtain order numbers, random seed numbers and grouping results. Then make a random card and seal it in an opaque envelope. Before preparing to start the clinical trial, the serial number will be used according to the order in which the subjects were included in the study, the order number on the corresponding envelope will be opened, and then grouped according to the prompts on the random card. The whole process ensures randomness and secrecy and reduces the bias of researchers.

6.3 Blind law

The study includes the blind design of patients and evaluators. Only acupuncture operators know. Intervention to be used. The treatment was carried out according to the individual's schedule, so no patient had any contact with other patients in the study. In addition, all patients agree not to contact other participants and avoid talking about their treatment.

7. Interventions

This study is divided into 2 The group is the electric needle group and the false needle group respectively. The place of acupuncture treatment is Department of Neurology, Dade Road Hospital, Guangdong Provincial Hospital of Traditional Chinese Medicine. Every week 2 Times, every time 30 Minutes of electric needles (true or false), continuous 1 Months in total 8 Times (the course of treatment is 30 Oh, my God).

1· Basic treatment and emergency plan

Before starting the designated treatment plan, the patient Accepted NMOSD Guidelines for the remission period (hormonal combined immunosuppressants (immunosuppressants include thiopurine, medicophenol ester or rithitoximab)) and/Accepted NMOSD Guidelines for patients with pain (pribalin, barclofen or

gabapentine), basic treatment during the study and guidelines for patients before grouping. In the next stage of the study, all patients will start their designated treatment plan. (Electric needle) This point in time is set to 1 Day, the treatment period is 30 Oh, my God. Patients record the daily intake and intensity of analgesic drugs required. (NRS) Standardized patient diary of pain parts.

2· Test group: electric needle group

Take acupuncture points: three miles of both feet (ST36), Sanyin sex (SP6), Hegu (LI4) and Quchi (LI11), insert the needle, insert the ninth needle into the seal hall (EX-HN3)

Acupoint location reference 2006 National standards of the People's Republic of China (GB/T12346-2006 Name and Positioning of Acupoints.

Operation process: The patient's position is supine. For acupuncturists 75% After disinfecting the acupoints on both sides of your hands and the subject, the double-sided acupuncture points will be covered with foam pads (1*1*1cm³). Acupuncture point adoption 0.25 × 0.25mm The disposable sterile acupuncture needle passes through the hollow tube and punctures into the acupuncture point through the foam adhesive pad. Acupoints, insertion angle and insertion depth are based on the references in the classic literature of traditional Chinese medicine. After taking the needle, the subjects will feel sour, numb and swollen in the local place. Connect the two electrodes of the electroneedle to the needle handle of the same limb acupuncture point., There is no positive or negative difference., Note that the metal surfaces of the two electrodes cannot be leaning against each other. Needle parameters: select sparse waves, The frequency is set to 4Hz The stimulation intensity is based on the patient's tolerance, and the needle retention time is 30 Minutes.

Control group: false needle group

Acupuncture points: acupoints used in the electric needle group Horizontal side 1cm Pay attention to avoiding traditional Chinese medicine. 14 Any corresponding area in the meridian.

Acupoint location reference 2006 National standards of the People's Republic of China (Generation B/T12346-2006 Name and Positioning of Acupoints.

Operation process: The patient's position is supine. For acupuncturists 75% After disinfecting the acupoints on both sides of your hands and the subject, the double-sided acupuncture points will be covered with foam pads (1*1*1cm³). All acupuncture points are used. 0.25 × 0.25mm The disposable sterile acupuncture needle passes through the hollow tube and punctures into the acupuncture point through the foam adhesive pad. The insertion of the needle is shallower (less than 0.2cm), it has a similar pain when a normal needle pricks into the needle. Connect the two electrodes of the electroneedle to the needle handle of the same limb acupuncture point., There is no positive or negative difference., Note that the metal surfaces of the two electrodes cannot be leaning against each

other. Needle parameters: select sparse waves, The frequency is set to 4Hz, the stimulation intensity is 0mA, the retention time is 30 Minutes.

8. Research steps

1. Screening period:

(1) The doctor will ask, record the medical history and the results of previous examinations, conduct a comprehensive physical examination of you, and the nurse will collect the patient. 3ml Blood routine, biochemical, liver function, IL6, TNF- α Examine and take blood samples, tongue coating samples and feces samples, and collect demographic information of subjects through the inpatient medical record system.

(2) Perfect EDSS, NRS Scales, MPQ Pain scale, SDS Depression Scale, SAS Anxiety Scale, SF-36 Quality of life scale.

(3) Perfect and collect head, neck and chest MR Scan and enhance relevant data to improve fMRI Check and collect relevant data.

2. Treatment period:

The electroacupuncture group will be treated with electroacupuncture on the basis of immunotherapy and basic analgesia, and the control group will receive false acupuncture treatment on the basis of immunotherapy and basic analgesia. Every week 2 Times, every time 30 Minutes of electric needles (true or false), continuous 1 Months in total 8 Times (the course of treatment is 30 Oh, my God). Patients fill in a pain diary every day, and the treatment is carried out by the same acupuncturist. The manufacturer and use of acupuncture acupuncture needles, fake acupuncture and electroacupuncture instruments are consistent.

3. Eighth post-treatment visit (group No. 28 ± 3 Day):

(1) Patients collected by nurses 3ml The blood is routinely tested for blood, biochemical and liver function, and blood samples, tongue coating samples and feces samples are retained.

(2) Perfect EDSS, NRS Scales, MPQ Pain scale, SDS Depression Table, SAS Anxiety Scale, SF-36 Quality of life scale.

(3) Perfect fMRI Check and collect relevant data.

In this study, blood samples, tongue coating specimens and fecal samples were used to explore. NMOSD The relevant mechanism of pain in patients and the mechanism of electroacupuncture in the treatment of pain in patients with optic neuromyelitis spectrum diseases, all samples will be frozen in the Biological Resources Center of Guangdong Provincial Hospital of Traditional Chinese Medicine and preserved. 3 The sample was destroyed after the study. All samples are only used for this study, and your relevant personal information will not be made public. Researchers, personnel of the Bioresource Center and the Ethics Committee will be allowed to have access to these samples, and

subjects can request withdrawal from the reservation or research of the sample at any time.

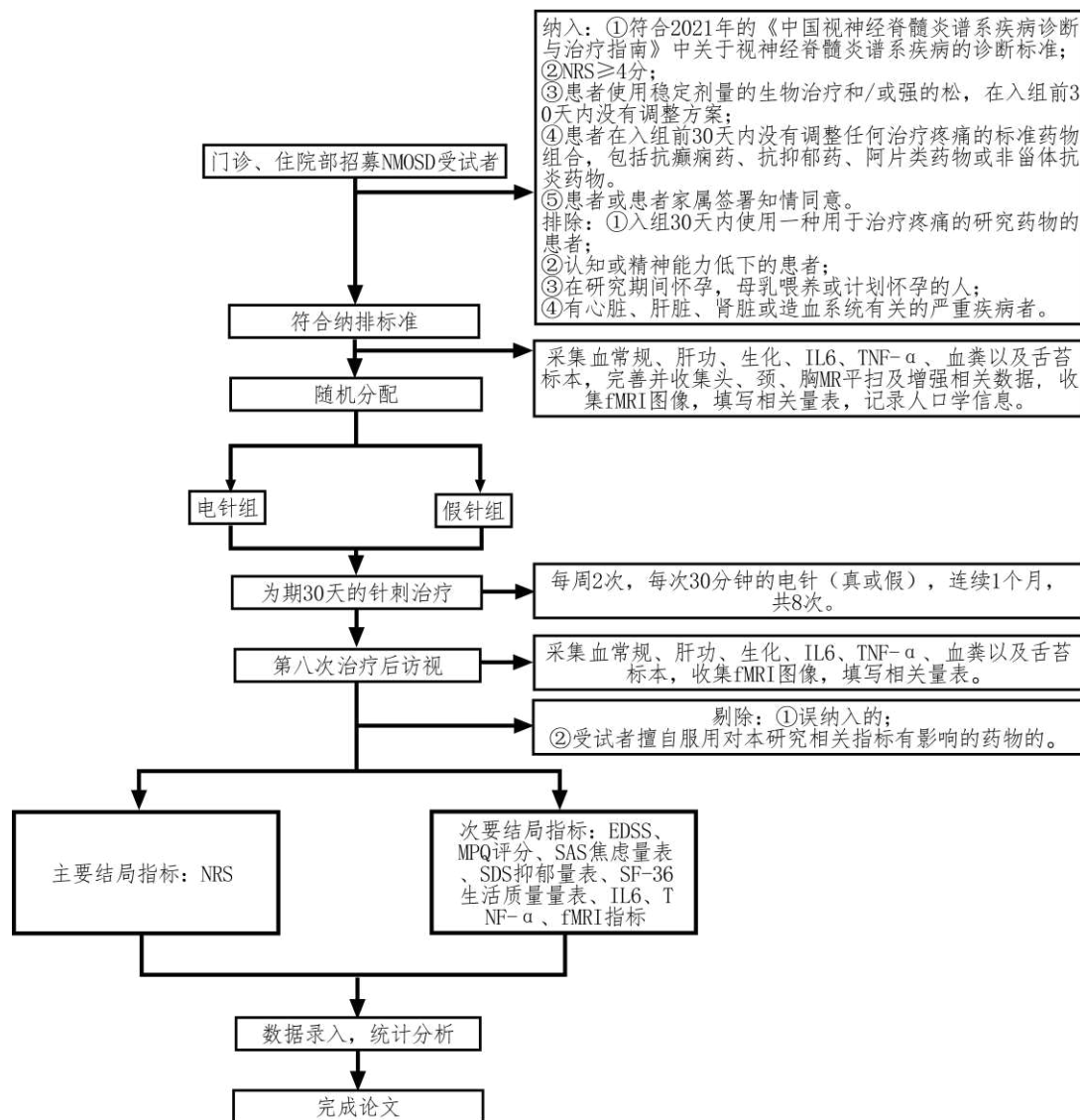
9. Outcome evaluation indicators

Main evaluation indicators: NRS

Pain sheet rating

Secondary evaluation indicators: EDSS、MPQ Rating, SAS Anxiety Scale, SDS Depression Scale, SF-36 Quality of life scale, IL6、TNF- α 、fMRI Indicators.

10. Technology roadmap



11.2.1 Common adverse acupuncture events/Reaction and treatment: Acupuncture has adverse reactions such as hematoma, stagnation needle, halo needle, etc.

1) Spend money/Hematoma: During acupuncture and acupuncture, local bleeding caused by puncture of blood vessels./Hematoma. Mild bleeding/Of Patients with hematoma can use disinfectant cotton swabs or cotton balls for local compression to stop the bleeding without special treatment. Moderate and severe bleeding/Patients with hematoma should be based on their bleeding./Take corresponding measures to the degree of hematoma, first stop the bleeding to prevent the increase of local swelling, carry out local anti-inflammatory treatment, and ask a surgeon to assist in dealing with it.

2) Stagnation needle: When acupuncture the stagnation needle, you should first relax the local tense muscles, and gently take the needle. Do not pull it hard. It can be opened next to the stagnant needle. 2 Enter the needle inch by inch, and then take out the stranded acupuncture needle. Severe needle stagnation should be assisted by a surgeon.

3) Needle halo: When the patient pricks the needle with acupuncture, he should quickly take out the needle and let the patient lie flat, lower his head, cushion his footsteps, and moxibustion his Baihui acupuncture point. After the patient's halo needle situation is slightly relieved, he can be ordered to drink a little warm boiled water. If the patient's needle is serious and he or she can't wake up, it should be treated according to syncope.

4) Infection: When there is redness, swelling and heat pain in the acupuncture area, the patient's affected part is told to rest and move less to reduce the spread of pain and inflammation, raise the limbs, promote reflux, reduce swelling, do not squeeze the affected part, and carry out local anti-inflammatory treatment. If necessary, you should ask a surgeon to assist in dealing with it.

11.2.2 Observation, recording and handling of adverse events

If the researchers found that the patient had adverse events caused by acupuncture/The reaction should be recorded in CRF Centre "Bad Events /Reaction record form" And for adverse events caused by acupuncture./Responding patients give enough comfort and treatment to make them have adverse events./The reaction should be eliminated as soon as possible. If there is a serious adverse event/In addition to the above treatment, the reaction should also be immediately reported to the Second Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine. There are adverse events in patients./Whether to continue the research after the reaction, first The patient's own will should be respected first, and the researchers who report adverse reactions should judge according to their professional knowledge.

11.3 Serious adverse events

11.3.1 Definition: Events that require hospitalization, prolonged hospitalization, disability, affecting working ability, endanger life or death, and leading to congenital malformations occur during clinical trials.

11.3.2 Report of serious adverse events

When there is a serious adverse reaction, it should be reported to Guangzhou University of Traditional Chinese Medicine within 24 hours of the second affiliated hospital and fill in the form of serious adverse events.

12. Data management and statistical analysis

Measurement data use: average \pm Standard deviation, median (M), maximum value, Minimum value, matching is used for comparison in the counting data group. T Test (Or pairing symbol rank sum test), variance analysis is used for inter-group comparison (non-normal distribution and variance irregularity are tested by rank sum (Kruskal-Wallis)) and two comparison and calculation 95% CI. The quantitative main outcome indicators of multiple observation time points are analyzed by repeated measurement. Rank sum test is used for comparison between hierarchical data groups (Kruskal-Wallis). The counting data is expressed by composition ratio and rate, and the comparison of total efficiency groups is expressed by cal-square test (or Fisher Accurate probability method). Intergroup composition Compared with comparison 2 \times C Table or 3 \times C Table cal-square inspection.

13. Confidentiality

The results of the research through this project may be published in medical journals, but we will keep the patient's information confidential in accordance with the requirements of the law. Unless required by relevant laws, the patient's personal information will not be disclosed. If necessary, government administrations and hospital ethics committees and their relevant personnel can consult patients' information as required.

14. Ethical standards

The program of this experiment, Case report form, The informed consent form should be approved in writing by the Ethics Committee of Guangdong Provincial Hospital of Traditional Chinese Medicine before it can be carried out.

The researcher or person authorized by the researcher will be responsible for explaining the benefits and risks of participating in the trial to each patient, the legal representative of the patient or notary witness, and shall obtain the patient's written informed consent during the screening examination.

All original informed consent co-signed and signed by the subjects or their legal representatives and the person presiding over the PIC process shall be kept by the researcher.

15. Study schedules

Starting and ending date	Main research content	Expected results
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<p>2021Year11Moon-- 2022Year01Moon</p>	<p>Consult domestic and foreign literature, sort out relevant data on electroacupuncture for pain treatment, establish diagnostic criteria, inclusion, exclusion and fall off of the topic, and make observation scales.</p>	<p>Carry out a literature review, establish a medical record report form and an opening report. Unify the clinical trial method and filling in the medical record report form.</p>
<p>2022Year02Moon-- 2022Year12Moon</p>	<p>Apply for ethical approval and register for clinical research, conduct clinical research, establish a database, manage various materials, and enter data.</p>	<p>Complete the clinical trial registration. Complete the medical record report form. Scientifically analyze the data and write statistical reports.</p>
	<p>Clinical summary, statistical analysis.</p>	
<p>2022Year12Moon-- 2023Year01Moon</p>	<p>Write a closing report and a paper.</p>	<p>Apply to close the topic and publish a paper.</p>