INPLASY PROTOCOL

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None declared.

Transcutaneous Electrical Nerve Stimulation in Rodent Models of Neuropathic Pain: A Meta-Analysis

Huang, JP[1]; Yang CL[2]; Zhao, KH[3]; Zhao, ZQ[4]; Chen, Y[5]; Wang, TT[6]; Qu, Y[7].

Review question / Objective: **Does transcutaneous electrical nerve stimulation (TENS) have an analgesic effect in rodent models of neuropathic pain?**
Eligibility criteria: **(1) Animal studies using rodent models of neuropathic pain induced by one of the following methods: chronic constriction injury (CCI), spared never injury (SNI), spinal cord injury (SCI), spinal nerve ligation (SNI), nerve crush injury (NCI), viral infection for postherpetic neuralgia, plexus ablation, chemotherapeutics, streptozotocin administration, or central lesions; (2) Rodents in experiment groups received all standard models of TENS with unlimited frequency, intensity, duration, and timing of intervention. TENS was not utilized in combination with another intervention; (3) Neuropathic pain-inducing rodents in the control group should receive sham TENS or blank treatment, except usual anesthesia; (4) Studies had to provide quantitative data on pain, irrespective of the type of pain, which can be measured by a mechanical threshold, thermal threshold, or cold threshold. And pain can be expressed as an absolute value or a percentage; (5) Literature is published in English; (6) Original full research paper, not review, editorial, and conference abstract.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 November 2021 and was last updated on 29 November 2021 (registration number INPLASY2021110104).

INTRODUCTION

Review question / Objective: **Does transcutaneous electrical nerve stimulation (TENS) have an analgesic effect in rodent models of neuropathic pain?**

Rationale: **Neuropathic pain, which is caused by an injury or disease of the**

somatosensory system, is characterized by spontaneous pain, hyperalgesia, and allodynia and can be classified as peripheral or central neuropathic pain according to the site of injury or disease. It is estimated that the prevalence of neuropathic pain is 6.9% to 10%. Neuropathic pain represents an important source of chronic pain and dysfunction and causes a significant burden on people and society. Therefore, the management of neuropathic pain should be important to ameliorate its negative impact on activities of daily living and quality of life. The mainstay of interventions for neuropathic pain is primarily pharmacological; however, for the large number of patients who cannot benefit from pharmacological intervention or who experience unwanted side effects, improving the ability to effectively relieve neuropathic pain with a non-pharmacological intervention such as psychological or physical treatment is crucial. TENS is a non-invasive therapeutic intervention that is typically used for many years to treat chronic pain in patients who are refractory to pain medications. However, evidence of the efficacy of TENS treatment for neuropathic pain is lacking in humans. To further understand the efficacy of TENS under various intervention conditions and illuminate the current circumstance and future research directions, we will systematically review animal studies investigating the efficacy of TENS in relieving pain in neuropathic pain models. Once the benefits are proven, it will provide a useful reference for clinical use in the future.

Condition being studied: Neuropathic pain.

METHODS

Search strategy: We have searched the following electronic bibliographic databases: Cochrane Library, EMBASE, MEDLINE (via PubMed), and Web of Science. The search string was built as follows: individually or combined included pain, transcutaneous electrical nerve stimulation, muridae, and a string of words that were determined after multiple pre-searches. No publication date restrictions. The language was limited to English.

Participant or population: Neuropathic pain rodent models.

Intervention: TENS with unlimited frequency, intensity, duration, and timing of intervention.

Comparator: Sham TENS, blank treatment, except usual anesthesia.

Study designs to be included: Controlled studies with a separate control group.

Eligibility criteria: (1) Animal studies using rodent models of neuropathic pain induced by one of the following methods: chronic constriction injury (CCI), spared never injury (SNI), spinal cord injury (SCI), spinal nerve ligation (SNI), nerve crush injury (NCI), viral infection for postherpetic neuralgia, plexus ablation, chemotherapeutics, streptozotocin administration, or central lesions; (2) Rodents in experiment groups received all standard models of TENS with unlimited frequency, intensity, duration, and timing of intervention. TENS was not utilized in combination with another intervention; (3) Neuropathic pain-inducing rodents in the control group should receive sham TENS or blank treatment, except usual anesthesia; (4) Studies had to provide quantitative data on pain, irrespective of the type of pain, which can be measured by a mechanical threshold, thermal threshold, or cold threshold. And pain can be expressed as an absolute value or a percentage; (5) Literature is published in English; (6) Original full research paper, not review, editorial, and conference abstract.

Information sources: We have searched the following electronic bibliographic databases: Cochrane Library, EMBASE, MEDLINE (via PubMed), and Web of Science. No publication date restrictions. In cases when data was not explicitly reported, we will extract data from figures using Engauge Digitizer. In cases of ambiguity, authors were contacted to provide additional information. Missing

data items will not be requested from authors as the data has not been peer-reviewed.

Main outcome(s): The primary outcome was pain threshold, irrespective of the type of pain, which can be measured by a mechanical threshold, thermal threshold, or cold threshold. And pain can be expressed as an absolute value or a percentage.

Additional outcome(s): The secondary outcomes included mortality and adverse events.

Quality assessment / Risk of bias analysis: The SYRCLE animal experiment bias risk assessment tool will be applied to evaluate the risk of bias in individual included studies. Two investigators will independently read the included literature and assess the risk of bias. Discrepancies will be resolved through discussion, or by consulting a third investigator. Studies will be divided into low-bias risk, high-bias risk, and unclear-bias risk.

Strategy of data synthesis: All meta-analyses and graphical displays will be conducted using Review Manager (RevMan) software (The Cochrane Collaboration, version 5.3). If methods of outcome measurement or forms of data expression were different among the included studies, a standardized mean difference (SMD) will be calculated using random-effects inverse variance meta-analyses and presented with 95% confidence intervals; otherwise, a mean difference (MD) will be used. To ensure that the results had the same directional value, we will multiply one kind of outcome by –1 if the change direction to reflect the relief degree of neuropathic pain was different. To prevent double-counting sample sizes of control animals, we will split the animal number of the control group in case of studies using a single control group and multiple experimental groups. For studies that could not be included in the meta-analysis, we will perform a descriptive summary.

Subgroup analysis: Where comparable data were available from at least three studies, we planned subgroup analysis in the following domains: frequency, the timing of intervention, intensity, electrode placement, species, method of modeling, the timing of outcome measurement, and anesthesia used during intervention procedures.

Sensitivity analysis: We will evaluate the robustness of the results using leave-one-out sensitivity analyses.

Language: English.

Country(ies) involved: China.

Keywords: transcutaneous electrical nerve stimulation, neuropathic pain, animal studies, pain models, meta-analysis.

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