INPLASY PROTOCOL

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None declared.

The efficacy effectiveness and safety adverse events of gabapentinoids after as analgesics for patients with burn injury: A systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: **(i) population: patient with burn wounds (ii) intervention: gabapentinoids (gabapentin, pregabalin, or mirogabalin) (iii) comparison: control group regimen (iv) outcomes: (a) pain score (b) opioid consumption, and (c) adverse effects.**
Condition being studied: **Burn-induced pain is noxious and often persists long after the initial injury, placing burdens on the patient and the healthcare system. The proposed mechanism of burn pain involves both the central and peripheral nervous systems with mixed features of nociceptive, inflammatory, and neuropathic pain. The selection of analgesics for burn-induced pain is often multimodal. Opioids remain the mainstay of pharmacological treatment for burn pain, but they should be tailored to avoid tolerance, opioid-induced hyperalgesia, and overdose. On the other hand, pregabalin and gabapentin are γ-aminobutyric acid analogues that bind to the α2δ protein, which inhibits calcium influx and the release of excitatory neurotransmitters. The antinociceptive and anxiolytic effects of these gabapentinoids have been utilized in different peripheral neuropathic pain syndromes, but their role in post-burn pain management is still under debate. Therefore, we conducted this systematic review with meta-analysis to provide more insights into the role of gabapentinoids after burn injury.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 January 2023 and was last updated on 03 January 2023 (registration number INPLASY202310007).

INTRODUCTION

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Rationale: Pain after a burn injury is difficult to sustain and requires proper treatment during daily wound care and procedures. Analgesics for burn injury are often multifaceted, and emerging studies are trying to ascertain the effect of gabapentin and pregabalin as non-opioid treatment options. We aim to perform systematic review with meta-analysis for assessment both benefits and disadvantages of gabapentinoids for patients with burn injury.

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METHODS

Search strategy: Two authors (LJ Chiang and YT Huang) performed a systematic search without language restrictions on PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), China National Knowledge Infrastructure (CNKI) and Google Scholar for randomized controlled trials (RCTs) that compared gabapentionoids with control in post-burn patients from the inception up to December 30th, 2022. We used both hierarchical search terms (e.g., Medical Subject Headings) and text word terms to search for articles about “burn pain”, “post-burn”, “pain”, “gabapentin”, “pregabalin”, “mirogabalin” and “analgesics”.Two authors (LJ Chiang and YT Huang) performed a systematic search without language restrictions on PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), China National Knowledge Infrastructure (CNKI) and Google Scholar for randomized controlled trials (RCTs) that compared gabapentionoids with control in post-burn patients from the inception up to December 30th, 2022. In addition, we searched ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials Database for any ongoing or unpublished trial. We used both hierarchical search terms (e.g., Medical Subject Headings) and text word terms to search for articles about “burn pain”, “post-burn”, “pain”, “gabapentin”, “pregabalin”, “mirogabalin” and “analgesics”.

Participant or population: Patient with burn wounds.

Intervention: Gabapentinoids (gabapentin, pregabalin, or mirogabalin).

Comparator: Control group regimen.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Studies were excluded if they met one or more of the following criteria: 1) article types including review articles, case reports, case series, retrospective data analyses and non-randomized prospective studies; 2) no available or relevant data for meta-analysis; 3) trials compared with any other analgesics in the control group instead of gabapentinoids; 4) pharmacological or non-

thermal pain model; 5) duplicated publications.

Information sources: We also searched ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials Database for any ongoing or unpublished trial.

Main outcome(s): The primary outcomes were pain scores and opioid consumption up to 3 weeks after burn injury. Secondary outcomes were adverse events after administration of gabapentinoids compared to control group. Any pain score and daily opioid consumption within two weeks of enrolled studies were extracted. We further subdivided them into 3 groups: within 24 hours, from 72 hours to 9 days, and 3 weeks. Adverse events of gabapentinoids were calculated, included dizziness, drowsiness, nausea, diarrhea, constipation, urinary retention, and pruritus.

Quality assessment / Risk of bias analysis: The risk of bias was assessed by two authors (YT Huang and PC Lai) independently using the Risk-of-bias tool 2.0 (RoB2). The results of RoB2 were drawn using the "Risk-of-Bias Visualization tool". The certainty of evidence was assessed by using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.

Strategy of data synthesis: A data collection form was specifically developed for this review and two authors (LJ Chiang and YT Huang) independently evaluated the full manuscripts of all included trials and performed data extraction. Data extracted from trials included demographics, drug administration, sample size, number of patients in treatment groups, follow-up period, pain scores, opioid consumption, and adverse events. We extracted values from graphs for unavailable numerical data. Dichotomous and continuous outcomes were presented as risk ratio (RR) and mean difference (MD), respectively, with 95% confidence intervals (CIs).
Statistical analysis was performed using Review Manager (RevMan) version 5.4.1 (The Cochrane Collaboration, London, United Kingdom). We utilized the random-effects model for the continuous data and the inverse variance heterogeneity (IVhet) model for dichotomous data using Microsoft Excel (Microsoft, Redmont, WA, United States) add-in MetaXL 5.3 (EpiGear International, Sunrise Beach, Australia). Heterogeneities among studies were assessed using the I square (I2) statistics. An I2 higher than 50% represented substantial heterogeneity. We assessed statistical heterogeneity with the I2 statistic and Cochran's Q. For each outcome, we performed further subgroup analysis according to different analgesics. Subgroup analysis was performed using the Q-test. Publication bias was assessed using the Doi plot and Luis Furuya-Kanamori asymmetry (LFK) index for each endpoint. An LFK index out of ±1 was defined as asymmetry of Doi plot and indicated the presence of publication bias.

Subgroup analysis: We further subdivided them into 3 groups: within 24 hours, from 72 hours to 9 days, and 3 weeks.

Sensitivity analysis: For sensitivity analysis of zero events in adverse events, we utilized random-effects model Bayesian approach.

Language restriction: No language limitation.

Country(ies) involved: Taiwan.

Keywords: Burn; pain; gabapentinoid; gabapentin; pregabalin.

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