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Pregabalin may reduce neuropathic pain in burn victims

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ABSTRACT A clinical decision report using:

Gray P, Kirby J, Smith MT, et al. Pregabalin in severe burn injury pain: a double-blind, randomized placebo-controlled trial. *Pain*. 2011;152(6):1279-1288. <https://doi.org/10.1016/j.pain.2011.01.055>

for a patient with burn injury pain.

Keywords: *pregabalin, burn, neuropathic pain*

Clinical-Social Context

Ms. Anna Grant (pseudonym) is a white woman in her 50s who presented to the Emergency Room of an urban level 1 trauma center with extensive thermal burns to the arm, forearm, hand, and fingers of a single upper extremity following contact with hot liquid. Ms. Grant has a past medical history significant for fibromyalgia. She is retired, resides in a home with family members in a middle-class neighborhood, and states that she has adequate social and financial support. Evaluation of her burns revealed Total Body Surface Area (TBSA) affected approximately equal to 5.2%: 4.0% was deep partial thickness, and 1.2% was full thickness. Given the extent of her injury, her care team recommended surgical debridement and temporary xenograft placement, with future plans for superficial thickness skin grafting.

Two weeks after her injury, Ms. Grant complained of persistent “burning” and “sharp tingling” in her affected extremity. She had previously been prescribed 0.5 milligrams of dilaudid once every four hours for pain. However, she inquired whether a non-opioid medication could be used to control her pain instead. She had experienced side effects with dilaudid such as lightheadedness and drowsiness. Additionally, she expressed a desire to decrease her consumption of opioids, as she had witnessed high rates of opioid addiction within her community. She denied a personal history of opioid use prior to this incident and a familial history of opioid addiction. Her treatment team wondered whether gabapentinoids, such as gabapentin or pregabalin, could alleviate Ms. Grant’s classic neuropathic symptoms and lower her requirement for opioid medications. Ms. Grant denied a history of gabapentinoid use. Pregabalin was chosen for investigation because it displays a favorable pharmacokinetic profile compared to gabapentin, such as earlier onset of clinical effect, linear absorption pharmacokinetics, and greater potency.¹

Clinical Question

Can pregabalin reduce neuropathic pain and reduce risk of opioid dependency in burn victims?

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Research Article

Gray P, Kirby J, Smith MT, et al. Pregabalin in severe burn injury pain: a double-blind, randomized placebo-controlled trial. *Pain.* 2011;152(6):1279-1288. <https://doi.org/10.1016/j.pain.2011.01.055>¹

Description of Related Literature

A PubMed search was performed using the terms “pregabalin” AND “burn”, yielding 21 results. Each article was reviewed with the goal of identifying a randomized control trial that would address our clinical question.

Of the 21 PubMed results, eight were unrelated to the clinical question and immediately excluded.³⁻¹⁵ One result was a retrospective cohort study that identified risk factors in developing chronic neuropathic pain following hand burns.¹⁶ Three results investigated pruritis¹⁷⁻¹⁹, a subtype of neuropathic pain often experienced by burn victims. Chung et al. is a review that described the physiologic mechanisms underlying post-burn pruritis¹⁷, while Foroutan et al. and Ahuja et al. are reviews that investigated the antipruritic effects of pregabalin in burn patients.^{18,19} Both aforementioned studies concluded that pregabalin was effective in reducing post-burn pruritis. However, because Ms. Grant was not experiencing post-burn pruritis, these articles were excluded.

Kaul et al. was a retrospective chart review that studied the effects of gabapentinoids in reducing pruritis and other forms of neuropathic pain in pediatric burn victims.²⁰ The authors found gabapentin and pregabalin to be highly efficacious. However, this study was ultimately excluded as it was not a randomized controlled trial, and did not address whether pregabalin would reduce opioid consumption. Additionally, Ms. Grant would not have fit inclusion criteria for this study on the basis of her age.

Wong et al. is another retrospective chart review conducted upon patients experiencing post-burn neuropathic pain.²¹ 69% of patients who completed the study achieved pain score reduction after three weeks or less of treatment with pregabalin. However, like Kaul et al., this study was also excluded as it was not a randomized controlled trial and did not address the effect of pregabalin on patients’ opioid consumption.

The two remaining articles (Jones et al. and Gray et al.) were randomized, double-blind, placebo-controlled studies investigating the efficacy of pregabalin in reducing neuropathic pain and opioid consumption in burn victims.^{22,2} Jones et al. was a study conducted on 54 burn patients with a median TBSA affected of 5%.²² Patients were randomized into three treatment groups: pregabalin 300 mg daily, pregabalin 600 mg daily, and placebo. Post-burn pain levels were measured using the 10-point Visual Analog Scale. Additionally, opioid consumption was recorded either during the first three days of treatment or until the patient was discharged, whichever came first. A statistically significant difference in post-burn pain levels was identified between the Pregabalin 300 and Pregabalin 600 groups. However, the difference in post-burn pain levels between both Pregabalin groups and the placebo group were statistically insignificant. In addition, the difference in opioid consumption between all three groups was statistically insignificant. This study had shortcomings, including a high participant attrition rate following discharge from the hospital and limited data collection following an unanticipated change in the standard of care for burn patients at the investigators’ institution, leading to shorter hospitalization periods and decreased enrollment.

The second study, Gray et al., was conducted on 90 burn victims with 5% or greater TBSA affected.² Patients experiencing symptoms of neuropathic pain were randomized into two treatment arms, pregabalin or placebo. Patients in the pregabalin group received 75 mg of pregabalin twice daily, which could be up-titrated to 300 mg twice daily if pain scores remained high. Unlike Jones et al., post-burn pain levels were measured using the Neuropathic Pain Scale (NPS), an assessment tool that quantified participants’ perception of ten neuropathic pain symptoms. This allowed researchers to quantify how “hot” and “sharp” participants’ pain felt throughout the study. Gray et al. also studied opioid consumption throughout the 4-week trial.

Gray et al. was ultimately selected for critical appraisal. Compared with Jones et al., Gray et al. possessed larger treatment cohorts and lower attrition rates. Importantly, unlike Jones et al., Gray et al. utilized the presence of neuropathic pain, such as hot and sharp pain, as inclusion criteria for patient enrollment. Prior to concluding the literature search, additional searches were performed to ensure that all articles relevant to the clinical question were previously identified. To do so, a search for “Related Articles” associated with Gray et al. was performed within Google Scholar, and both Google Scholar and UpToDate were searched using the terms “pregabalin” and “burn,” yielding no novel results which addressed our clinical question.



This area of study has Strength of Recommendation Taxonomy (SORT) strength of recommendation B for limited quality, patient-oriented evidence.²³

Critical Appraisal

Gray et al. is a randomized, double-blind, placebo-controlled study investigating the efficacy of pregabalin in reducing neuropathic pain and opioid consumption in burn victims. While the authors did not disclose their source of funding, they declared no conflicts of interest in the design or conduct of the trial. This study qualifies as level of Evidence 1B per SORT criteria.²³

Patients between 18 and 65 years of age who were admitted to the Burn Unit of a large, tertiary referral hospital in Australia were screened for inclusion in the trial. Immediate exclusion criteria included less than 5% TBSA burned, regular use of antiepileptic drugs at the time of the burn injury, neuropathic pain prior to burn injury, administration of intravenous lidocaine or mexiletine after burn injury, allergy to gabapentinoids, and history of psychiatric illness or substance abuse. Patients who were not immediately excluded were subsequently screened for study entry by completing the NPS every day. If a patient rated either “hot pain” or “sharp pain” greater than or equal to 4, they were offered entry into the trial given that they were not pregnant and demonstrated a creatinine clearance greater than or equal to 60 milliliters per minute, liver enzyme levels within normal limits, and an Internationalized Normalized Ratio less than 1.5. Ultimately, 90 patients were enrolled in the trial. Given her past medical history and the quality of her neuropathic symptoms, Ms. Grant would have qualified for enrollment. Information regarding the participants’ past medical histories, including chronic pain conditions, was not provided. Most of the study participants were younger than Ms. Grant (mean age of 35.7 with S.D. of 12.8), and most were male (83.3%). The mean TBSA burn for participants was not provided. Like Ms. Grant, 75.5% of participants had burns severe enough to warrant skin grafting.

Participants were randomized into two cohorts for the duration of the 28-day trial. 46 participants entered the pregabalin arm, while 44 participants entered into the placebo arm. The staff and researchers were blinded to the group allocation for the duration of the study. This sample size was sufficient to obtain a significance level of $\alpha=0.05$. Initially, patients received 1 capsule (75 mg pregabalin or placebo) by mouth twice daily. Patients continued on this regimen unless they rated their perception of “sharp pain” or “hot pain” on their daily NPS greater than or equal to 4. If this occurred, their medication was increased to 150 mg pregabalin or placebo twice daily. If they rated their perception of “sharp pain” or “hot pain” greater or equal to 4 on any subsequent day, their medication was increased to the maximum dose of 300 mg pregabalin or placebo twice daily. It should be noted that pain scales including the NPS do not provide an objective measure of pain, as pain considered mild by one participant might be considered severe to another. Additionally, patients completed their daily NPS alongside blinded research nurses, who could have introduced observer bias. After 28 days, medications were weaned and stopped. Primary outcome measures included the “sharp pain” and “hot pain” scores on the NPS. Additional outcomes measured included the remaining elements of the NPS, daily opioid requirement, procedural pain score, side effect profile, and persistence of pain at a 6-month follow-up. The study attempted to maintain a standardized regimen with regard to analgesic administration. However, opioids were administered in various routes depending on patients’ individual needs. As investigators noted, an ideal approach would have been to provide all patients with an intravenous morphine patient-controlled analgesia device for the duration of the 28-day trial. However, this would have been impractical and increased the risk of intravenous line infection. Overall, the pregabalin arm had a 73% retention rate while the placebo arm had a 75% retention rate.

Participants in the pregabalin arm demonstrated statistically significant improvements in sharp and hot pain compared to placebo during the trial ($P=0.04$ and $P=0.01$ respectively). Additionally, investigators noted a statistically significant improvement in procedural pain in patients who received pregabalin versus placebo ($P=0.02$). The average daily Morphine Parenteral Equivalent (MPE) dose for each 7-day period of the trial showed a statistically significant decrease in opioid requirement within either cohort, reflecting patient recovery. However, differences in opioid consumption between the placebo and pregabalin groups were not statistically significant ($P>0.05$). The difference in frequency of side effects between the pregabalin and placebo groups and persistence of pain 6 months after injury was statistically insignificant.

Clinical Application

Two weeks after sustaining a burn injury, Ms. Grant complained of bothersome sharp and burning sensations in her affected upper extremity, similar to those experienced by participants in Gray et al. Additionally, Ms. Grant was hesitant to continue taking opioid medications, citing unpleasant side effects, as well as risk of developing



opioid addiction, which she previously observed in her community. Gray et al. found pregabalin to be successful in decreasing symptoms of neuropathic pain similar to ones that Ms. Grant was experiencing. It did not, however, address the effect of pregabalin in patients with chronic pain syndromes like fibromyalgia, limiting its applicability to Ms. Grant. Additionally, Gray et al. did not demonstrate a statistically significant decrease opioid consumption among pregabalin and placebo cohorts. Ms. Grant was informed that pregabalin had demonstrated effectiveness in reducing the “hot” and “sharp” pain that she was experiencing in her hands, but that data was unclear regarding its effect on patients’ opioid consumption. Ultimately, Ms. Grant stated that she would be interested in trying pregabalin in order to combat her neuropathic symptoms, which she found highly uncomfortable.

New Knowledge Related to Clinical Decision Science

Burn pain can be multifactorial in nature and challenging to treat. The emergence of the opioid epidemic in the United States poses an additional hurdle for physicians treating pain, prompting them to weigh the short-term benefit of improved pain control against the long-term risk of addiction. Utilizing a personalized, multimodal approach can help providers better control patients’ pain levels while respecting their psychosocial needs. For example, in the case of Ms. Grant, identifying the presence of neuropathic pain allowed her treatment team to explore additional pharmacologic measures for pain relief. Additionally, refusal to explore adjunctive medications would have been insensitive considering her past experiences with opioid addiction in her community. Based on results from Gray et al., pregabalin may be an enticing treatment option for burn victims experiencing symptoms of neuropathic pain. However, further data is warranted to demonstrate its ability to lower opioid consumption, as well as its efficacy in patients with chronic pain syndromes, such as fibromyalgia.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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