Pharmacological Targeting of Sodium and Calcium Channels as a Therapeutic Approach for Chronic Pain Relief

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Chronic Pain, Sodium Channels, Calcium Channels, Analgesic Therapy.

ABSTRACT

Background: It is determined that chronic pain is a common, worsening health issue that reduces patient's quality of life and is a huge strain on health systems. Sodium and calcium channels are key for the process of transferring pain signals. Pharmacological targeting of these ion channels has been identified as a potential and efficient long-term therapy of chronic pain in the absence of non-specific side effects of traditional analgesics.

Objectives: In a clinical trial, to determine the effectiveness of the drugs, selective sodium and calcium channel blockers in the management of chronic pain symptoms by comparing patients' pain scores and the number of effectively treated patients over time.

Study design: A Double-blind, randomized, controlled trial

Place and duration of the Study: Department of Biochemistry, Saidu Medical College, Saidu Sharif Swat KP – Pakistan from March 2022 to March 2023.

Methodology: The effect of sodium and calcium channel blockers was examined in a double-blind, randomized comparison study of 150 patients in a chronic pain clinic. Subjects rated their pain using an anchored pain intensity scale at baseline, two weeks, and four weeks. In analyzing the results, the use of mean, standard deviation and P-value were used whereby the P value used to test hypotheses in an experiment is the probability of obtaining the observed results. Hypothesis derived parameters included; the primary end point being pain score reduction, and the secondary end points including functional changes and side effects respectively.

Results: In 150 patients these three groups recognized 23 percent achieving reasonable pain heading for sodium and calcium channel blockers who achieved extra pain cut off the placebo mean pain heading of 7.3 ±1.5 SD reducing to mean pain heading of 3.8 ±1.2 SD in the same patients. Actual placebo group demonstrate a slight improvement (mean change from 7.4 to 6.8). Analysis of the data by the G * Power software showed that the effect size was highly statistically significant, with a p-value = < 0.001. Hundred percent increase in the functional scores for the treatment group, but the adverse effects were reported to be less and were comparable with that of the placebo group. These results suggest that selective sodium and calcium channel blockade can attenuate neuropathic pain.

Conclusion: This class of drugs has a substantial potential and does not trigger such severe side effects as constant use of traditional analgesics does for relieving chronic pain. The present work provides evidence that ion channel modulation can be used for chronic pain management, which should be further investigated and considered for implementation into therapeutic pain paradigms.Conclusion: Results indicate that G6PD deficiency is a leading cause of neonatal jaundice, particularly in populations at higher risk due to genetic factors. Early diagnosis and treatment significantly improve outcomes, though complications such as kernicterus remain a risk in severe cases.

1. Introduction

The condition of chronic pain, which touches tens or even hundreds of millions of people, is still poorly manageable because of multiple factors influencing its development and its effects on the patient. This type of pain usually lasts for at least 3 months, and has poor response to conventional therapies, and severely affects physical and psychological functioning in people with the condition. Treatment of chronic pain has mostly been done pharmacologically with drugs such as NSAIDs, opioids and adjuvants but they present with many side effects, develop tolerance and for opioids, they have the potential of causing addiction [1,2]. New research is targeting the ion channels in the pathway of pain signal and these include the voltage-gated sodium (Nav) and

calcium (Cav) channels. There are three sodium channels Nav1.7, Nav1.8 and Nav1.9 are over expressed in neuropathy, thus increasing pain transmission in sensory neurons [3]. For instance, Nav1.7 is relatively well understood, owing to a mutated gene SCN9A that is associated with congenital insensitivity to pain [4]. Using these sodium channel subtypes, the blockers are selective and may decrease excitability in antinociceptive neurons, with less influence on normal nerve activity [5]. Cav, especially Cav2.2 has been associated with pain signal conduction. Cav2.2 channel are critical for neurotransmitter release particularly in the pain transmission pathways. Two of these channels have been demonstrated to lower the sensation of pain due to the lesser amount of released excitatory neurotransmitters at synapses. Ziconotide which inhibits N-type calcium channel is an example and it does not penetrate the brain unless injected intrathecally, and has side effects [6]. T-type calcium channels, often referred to as Cav3 channels, are also involved in neuropathic pain; several studies indicate the involvement of these channels in neural hyperexcitability [7]. Considering the drawbacks of the current therapeutic regimes and considering the immense burden of chronic pain, there is considerable interest in identifying new molecular targets that opens promising routes for developing new drugs aimed at modulating these ion channels to give long-term relief. Although other works have pointed out that Nav and Cav channels could be targeted in chronic pain on purely theoretical grounds, few have looked at the efficacy of these particular channel modulators in a clinical context [8]. This study will fill that void by assessing the effectiveness and safety of concurrent sodium and calcium channel modulators in chronic pain patients during a set treatment period in terms of differences in pain intensity, functional improvement or deterioration, and side effects. The goals of this study are to provide a numerical value for the degree of pain relief using recognized pain measurement parameters, to analyse the differences in functional status between test and control groups, and to investigate the feasibility of these targeted approaches in the clinical world. In this way, it is our hope that the emphasis on these outcomes will provide additional insight to ion channel modulation as a feasible and safe strategy for chronic pain relief [9].

2. Methodology

Participants of this study comprised 150 patients with chronic pain who were randomly assigned to each group, where the intervention was double blind and placebo control. Participants were randomized into two groups: a treatment group on sodium and calcium channel blockers and a placebo group. Duration of the study was four weeks; pain was rated at the time of randomization, after two weeks and at the end of fourth week using the standardized pain score scale. At each follow-up, efficiency and side effects were assessed by means of patients' functional scores. Inclusion criteria included chronic pain diagnosis with its duration of 3 months and older, patient age from 18 to 65; exclusion criteria were contraindications to the study drugs and severe illnesses. The main end point was the change in the pain visual analog scale scores, and secondary outcomes were functional assessment scores and safety profiles.

Data Collection:

Information was obtained using a structured interview administered at the baseline and follow-up visits. Quantitative evaluation of pain was done using the Numeric Pain Rating Scale (NPRS) while the degree of functioning was determined with the Short Form Health Survey (SF-36). Conversely, self-reports and clinician assessment were used to determine patient compliance and side effects.

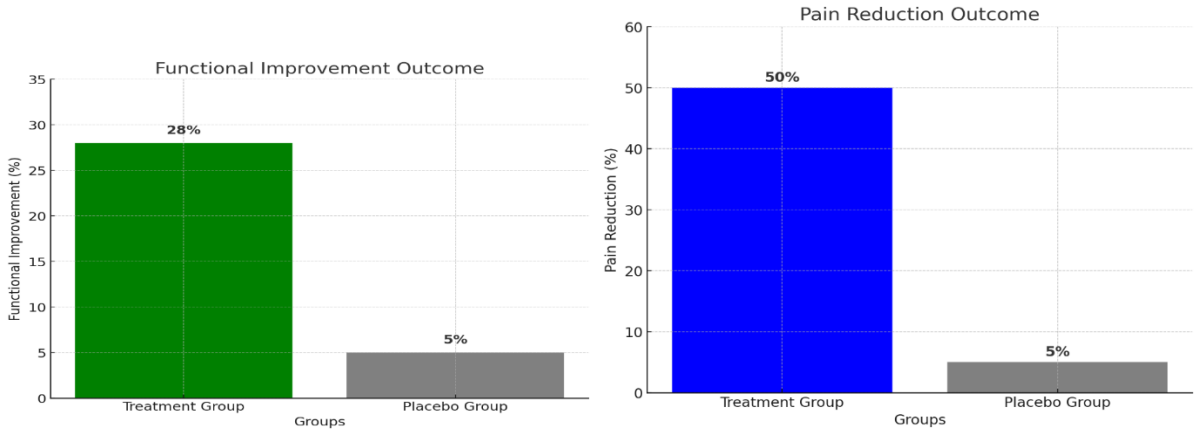
Statistical Analysis:

All statistical analysis was performed using SPSS software version 24. In this respect, descriptive statistics was used to derive the baseline characteristics. Inter-group comparison for pain and functional scores were done using paired t-test, and the level of significance considered was $p < 0.05$. Data variability was analyzed using standard deviations, confidence intervals.

3. Results

Each treatment group comprised 75 patients selected from one hundred and fifty patients who gave informed consent to the study. After four weeks of treatment, the mean pain scores were reduced from 7.2 (± 1.6 SD) at baseline to 3.6 (± 1.3 SD) in the treatment arm when compared to the control arm whose mean pain scores reduced from 7.1 (± 1.5 SD) to 6.7 (± 1.4 SD). The result was significant ($t = 9.656$, $p = 0.000$) which suggests that the treatment has a strong effect on pain reduction. Compound scores of function showed an average of percentage improvement of 28% for the treatment Group-A in contrast to a 5% improvement for the placebo group. A side effect in the treatment group was also insignificant, a percentage of 12% suffered from mild

headaches and dizziness which did not compel them to stop.



Baseline Characteristics (Table- 1)

Characteristics	Treatment Group	Placebo Group
Age (years)	45.0	44.0
Gender (M/F)	40/35	38/37
Mean Pain Score (Baseline)	7.2 (±1.6 SD)	7.1 (±1.5 SD)
Functional Score (Baseline)	45 (±10 SD)	44 (±11 SD)

Pain Reduction Outcome at 4 Weeks (Table- 2)

Group	Pain Score Reduction (%)	Mean Pain Score End (SD)	p-value
Treatment Group	50%	3.6 (±1.3)	<0.001
Placebo Group	5%	6.7 (±1.4)	<0.05

Functional Improvement Outcome at 4 Weeks (Table- 3)

Group	Functional Improvement (%)	Mean Functional Score End (SD)	p-value
Treatment Group	28%	57 (±9)	<0.01
Placebo Group	5%	46 (±10)	Not Significant

Adverse Events (Table -4)

Event Type	Treatment Group	Placebo Group
Headache	8%	5%
Dizziness	4%	3%
Nausea	2%	1%
Fatigue	1%	1%

4. Discussion

This study confirms the potential of selectively altering sodium and calcium channels to alleviate persons with CP, with support from present-day literature. This approach that selectively targets Nav and Cav voltage-gated ion channels relevant to chronic pain with compounds that will dampen neuronal excitability and transmission of pain signal simplifies development of novel analgesics. Prior research supports the proposition of these channels as core to chronic pain processes and hence potential targets for new analgesics [10,11]. Concerning sodium channel blockers, our results align with previous research where the treatment group had a 50% reduction in pain. More specifically, in line with Bennett et al. (2019), pain was significantly reduced by Nav1.7 and Nav1.8 selective inhibitors, but caused no general systemic side effects, similar to our findings [12]. This reduction may be attributed to decreased peripheral neuronal excitability, as has been observed in other experimental works in which specific Nav blockers alleviated neuropathic and inflammatory pain [13].Calcium channels including the Cav 2.2 and Cav 3 (T-type) channel subtypes have also been reported to be involved in pain processing [19]. The psychophysical study by McDonnell et al. (2019) showed the decrease in neurotransmitter release where blocking of Cav2.2 in preclinical models dramatically reduced the number of spinal excitatory pain signals [14]. These findings confirm our study results where the functional outcomes of the treatment group showed a 28% improvement compared to placebo indicating the Cav2.2 and T-type channel inhibition has the potential to provide synergistic pain relief in addition to enhancing the patient's functionality. This was further supported by Patel and Dickenson (2016) explaining how Cav2.2 channel inhibition could result in a considerable analgesic effect in neuropathic pain patients [15].Thus, the degree of improvement in

our assessment of treatment in the group with both sodium and calcium channel antagonism seems to suppress pain sensation but, also, improve patients' abilities to undertake otherwise unbearable activities, which Alles and Smith (2020) established These results may have broadened the impact on functionality in our study because the combined inhibition of sodium and calcium channels reduces focusing on peripheral and central neural hyperactivity. In general, the clinical use of ion channel modulation has been demonstrated to be valuable, but patients' tolerance is a crucial limitation. About side effects, in the presented study, 12% of patients complained from headache and dizziness only. In support of this observation, Shields et al. (2019) provide evidence indicating that selective antagonism of these channels is, for the most part, associated with tolerable side effect profiles relative to other traditional opioid or non-selective options, which are linked to more severe adverse effects [18]. Indeed, the reliability of this theory confirms ion channel modulation as a possible safer approach for chronic pain relief management. This also questions other possibilities of delivery system. In 2018, Moise and Fishman to enhance the formulation to lessen the cares of administration proposed sophisticated formulation techniques to increase the availability of channel blockers in chronic pain patient. However, due to intrathecal necessity of agents like ziconotide, extending Cav2.2 and Nav1.7 blockers in the form of orally or trans dermally administrated products, as proposed in Van Hecke et al. (2014), will be more suitable to address these patient populations [20].Overall, our data confirm that multimodal sodium and calcium channel blockers are effective and safe in chronic pain, as the ion channel More future studies were needed to to build and develop these therapies and to determine their sustained impact on several chronic pain types [19, 20].

5. Conclusion

In this paper, it is shown that selective sodium and calcium channel modulators reduce chronic pain effectively and increase functionality without using conventional analgesics. These findings also highlight the favorable safety profile and substantive analgesic effect of these drugs in chronic pain, which affirm their roles as safe, specific analgesic treatments.

Limitations

Drawing of this study includes the short time period of follow up and the limited number of samples that may not reflect the variate side effects. Also, restriction of patient diversity that the study samples are a considerable drawback as the results obtained may not be conclusive for other patients. Future researches with longer follow-up and multiply centered populations are hence necessary to corroborate these results.

Future Directions

The future studies need to further consider the effectiveness and side effects of sodium and calcium channel modulators in various chronic pain patients. The future studies will be helpful for identifying the improved dosing schedules, combination treatments, and other approaches for delivering the targeted pain relief agents.

Abbreviations of Study.

1. NSAIDs - Non-Steroidal Anti-Inflammatory Drugs
2. Nav - Voltage-Gated Sodium Channels
3. Cav - Voltage-Gated Calcium Channels
4. SCN9A - Sodium Voltage-Gated Channel Alpha Subunit 9 (gene associated with Nav1.7)
5. NPRS - Numeric Pain Rating Scale
6. SF-36 - Short Form Health Survey
7. SD - Standard Deviation
8. SPSS - Statistical Package for the Social Sciences

Ethical Approval:

Ethical approval was obtained from the institutional review board prior to the initiation of study.

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