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LETTER TO THE EDITOR

Exploring the analgesic effects of pregabalin for post-chikungunya arthralgia: a comparative double-blind study

Dear Editor,

Chikungunya represents a debilitating syndrome triggered by a homonymous virus. Its predominant clinical manifestation involves arthralgia coupled with physical limitations, mirroring rheumatoid arthritis.[1] Despite the absence of disease-specific therapies, the joint pain accompanying chikungunya is inflammatory in nature and exhibits neuropathic characteristics. Pregabalin has displayed beneficial effects, even among patients not meeting neuropathic pain criteria.[2] Notably, preceding research underscores the role of cytokines in the development of chikungunya-associated joint disease, akin to that seen in rheumatoid arthritis. This suggests potential benefits from immunomodulatory therapies such as hydroxychloroquine.[3] Given the disease's prevalence and the consequent morbidity, the necessity for more efficacious treatment options for chronic chikungunya-related arthralgia remains unmet.

This double-blind study compares a combined regimen of pregabalin and hydroxychloroquine (PH group) against a placebo and hydroxychloroquine regimen (H group) for managing chronic chikungunya. The primary focus is on pain intensity, with supplementary analgesic requirements, Quality of Life (QoL), and adverse events as secondary outcomes. The study received ethical approval from the institutional Research Ethics Committee (CAAE 34247020.6.0000.5505) and was registered with the Brazilian Registry of Clinical Trials (REBEC RBR-6mkndk). All participants provided informed consent, and allocation occurred via the Randomizer® program. Pregabalin capsules were indistinguishable from placebos. Both researchers and patients were blinded to the allocated treatment. Sample size determination was based on a two-tailed hypothesis test with 80% power, significance level of 5%, and a minimum mean difference of one point on the visual analog scale for pain. This resulted in a calculated sample size of 16 individuals per group. Inclusion criteria encompassed chronic chikungunya-related arthralgia of at least 3 months duration, confirmed diagnosis by serology (ELISA IgM-/IgG+), age 18 or older, any gender, and a referred pain intensity score of ≥4. Exclusion criteria included a history of rheumatoid arthritis, cognitive impairment, psychiatric disorders, drug hypersensitivity, illicit drug use, or pregnancy.

The PH group received a daily dose of 75 mg pregabalin for the initial 5 days, followed by 75 mg twice daily, alongside hydroxychloroquine at 400 mg/day for a total of 3 months. Conversely, the H group received placebo alongside hydroxychloroquine at the same dosage. Supplementary analgesia involved dipyrone (1 g) as needed, with a maximum recommended dose of 6 g/day. Patients experiencing inadequate pain relief were permitted to use tramadol (50 mg) up to a maximum of 400 mg/day.

Conducted at an outpatient medical center in Açailândia, Brazil, the study assessed pain intensity and QoL at baseline, 2 weeks, and months 1, 2, and 3. The study also tracked supplementary analgesia use and adverse effects. Pain intensity evaluations used a verbal numerical scale ranging from 0 to 10. Quality of life was evaluated using the WHOQOL-100 questionnaire. For statistical analysis, the Mann-Whitney test and Fisher's exact test were employed, with a significance level of ≤0.05.

Initial randomization allocated 18 participants to the PH group and 17 to the H group. However, one participant from the H group was lost to follow-up, yielding 18 and 16 evaluable participants in the PH and H groups, respectively. Statistical analysis revealed no significant inter-group differences in pain intensity, supplementary analgesia use, QoL, or the incidence of adverse events during the specified time points (Table 1).

Analgesic medication to manage chronic chikungunya-related arthralgia hinges on existing treatment approaches for other chronic joint conditions.[4] The pathogenesis of chikungunya arthralgia bears resemblance to that of rheumatoid arthritis, making hydroxychloroquine's efficacy in reducing inflammation pertinent.[3] While drugs targeting neuropathic pain have been proposed for refractory chikungunya-related arthritis, these recommendations largely stem from extrapolations and limited prior investigations.[5] Despite the potential merits of pregabalin, its use did not yield observable benefits in the current study. This could be attributed to the effectiveness of conventional analgesic

Study conducted at the Universidade Federal de São Paulo; Rua Botucatu 740; Vila Clementino, São Paulo, SP, Brazil; Postal code: 04023-900.

Link to the study registry: https://ensaiosclinicos.gov.br/observador/submissao/sumario/10097

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Table 1 Comparation between groups.

Variables	Group PH	Group H	*p*-value
Participant data – median (range)			
Duration of pain (years)	5 (3–7)	5 (2–8)	0.763[a]
Weight (kg)	73 (55–104)	73 (48–124)	0.276[a]
Height (cm)	1.6 (1.5–1.7)	1.6 (1.5–1.7)	0.245[a']
Number of joints	5.5 (2–12)	7 (2–14)	0.211[a]
Edema, n (%)	11 (68.8)	14 (77.8)	0.703[b]
Pain intensity at rest by numerical scale – median (range)			
T0	8 (4–10)	8 (7–10)	0.281[a]
2 weeks	5 (1–8)	6.5 (0–9)	0.515[a]
4 weeks	2 (0–7)	5 (0–9)	0.378[a]
8 weeks	0 (0–6)	0.5 (0–8)	0.101[a]
12 weeks	0 (0–8)	0 (0–9)	0.477[a]
Number of individuals who used supplemental analgesics – number (%)			
Dipyrone			
2 weeks	7 (38.9)	6 (37.5)	0.934[b]
4 weeks	9 (50.0)	7 (43.8)	0.716[b]
8 weeks	6 (33.3)	7 (43.8)	0.533[b]
12 weeks	4 (22.2)	6 (37.5)	0.329[b]
Tramadol			
2 weeks	6 (33.3)	8 (50.0)	0.324[b]
4 weeks	5 (27.8)	6 (37.5)	0.545[b]
8 weeks	7 (38.9)	7 (43.8)	0.774[b]
12 weeks	5 (27.8)	4 (25.0)	0.855[b]
Quality of life – median (range)			
Overall			
T0	62.5 (12.5–87.5)	46.9 (25.0–100.0)	0.175[a]
12 weeks	71.9 (25.0–100.0)	62.5 (25.0–100.0)	0.151[a]
Number of individuals who had adverse effects – number (%)			
Dizziness	5 (27.8)	2 (12.5)	0.405[b]
Drowsiness	3 (16.7)	4 (25.0)	0.681[b]
Abdominal pain	2 (11.1)	0 (0.0)	0.487[b]
Nausea	0 (0.0)	2 (12.5)	0.214[b]
Diarrhea	1 (5.6)	1 (6.3)	1.000[b]

[a] Mann-Whitney test.
[b] Fisher exact test.
Group PH, Pregabalin + hydroxychloroquine; Group H, Placebo + hydroxychloroquine; Quality of life, Evaluated by the WHOQOL-100 Questionnaire; NC, Not Calculated.

approaches, rendering pregabalin unnecessary. Moreover, the addition of pregabalin did not result in a heightened occurrence of adverse events. Concerning the dose of pregabalin, variability exists, with therapeutic utilization ranging from 25 to 600 mg/day, thus aligning with the dose implemented in this study. Future research should consider evaluating patients pre-screened for neuropathic pain to elucidate any potential role for pregabalin in managing chikungunya-related arthralgia.

In conclusion, the combination of 75 mg twice-daily pregabalin and 400 mg/day hydroxychloroquine over a 3-month period did not enhance pain control, quality of life, or decrease the need for supplementary analgesics in individuals with chronic chikungunya-related arthralgia.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval statement

Institutional Research Ethics Committee (CAAE 34247020.6.0000.5505) and registered in the Brazilian Registry of Clinical Trials (REBEC RBR-6mkndk). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent statement

Informed consent was obtained from all individual participants included in the study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.09.002.

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