Adjunctive Incremental Pregabalin Therapy Leads to Better Pain Relief in Patients With Chronic Pancreatitis

A Double-blind Randomized Controlled Trial

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Objectives: Gabapentinoids like pregabalin have been inadequately explored in patients with painful chronic pancreatitis (CP) on a long-term basis. The objective was to study the pain relief on pregabalin as an adjunct therapy for 12 weeks in painful CP.

Materials and Methods: In this double blind, randomized placebo-controlled trial, patients with painful CP with no ongoing inflammation(no pseudocyst/inflammatory head mass) or significant obstruction were randomized to receive either incremental doses of pregabalin or placebo for 12 weeks. The primary outcome was change in Izbicki pain score. Change in the quality of life (QoL) (SF-36 questionnaire), interference of pain with daily life [modified brief pain inventory- short form (mBPI-SF)] and patients' global impression of change (PGIC) were assessed as secondary outcomes. Tolerability and adverse effects were noted as safety outcomes. As an exploratory outcome, the role of quantitative sensory testing (QST) to predict patients' response to pregabalin was assessed.

Results: Fifty-five patients with painful CP (age 29.9 ± 10.6 y; 79% males; median illness duration 36 mo) were randomized to receive pregabalin (n = 30) or placebo (n = 25). Change in Izbicki pain score was significantly better in pregabalin group [pregabalin: −23.75 (IQR: −9.69 to −43.75) versus placebo: −8.75 (3.44 to −17.50); $P = 0.005$]. Overall QoL and PGIC were also better and interference of pain with daily activities reduced in the pregabalin group [median change BPI severity pregabalin: −1.83 (−0.83 to −3.75) versus placebo: −0.67 (0.33 to −1.42); $P = 0.008$; BPI interference pregabalin: −2.64 (−0.33 to −5.21) versus placebo: −0.43 (1.18 to −2.29); $P = 0.009$]. Frequent adverse events included sleepiness (51.7%) and giddiness (58%) but drug discontinuation occurred in only 10.4% of patients. No QST parameters could predict pain response to pregabalin.

Conclusions: Pregabalin is a useful adjunct to pain management in patients with CP.

Key Words: Chronic pancreatitis, Pregabalin, Pain-relief, Quality of life, Quantitative sensory testing

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Chronic pancreatitis (CP) represents a continuous fibroinflammatory process leading to progressive parenchymal destruction of the pancreas culminating in chronic pain, exocrine and endocrine insufficiency.[1,2] Pain in the abdomen is the most debilitating symptom in patients with CP requiring frequent hospital visits and hospital admissions and in turn significantly affects patients' quality of life(QoL).[3] The mechanisms of pain in CP are not well understood but they include ductal hypertension, oxidative stress, and ongoing pancreatic inflammation.[4] Increasingly, pain in CP is being recognized to be of neural origin, and neuropathy at both central and peripheral levels is being attributed to the pathogenesis of pain.[4] The recognition of neuropathic pain has been facilitated by quantitative sensory testing (QST), through which pain perception at both central and peripheral levels can be objectively assessed.[5]

The standard treatment of pain in CP includes opioid and non-opioid analgesics, antioxidants, endoscopic treatment and surgery.[1] In view of our increased understanding of the neural origin of pain, neuromodulators are increasingly being explored for pain management in patients with CP.[6] Drugs such as gabapentinoids (eg, pregabalin) are effective in multiple neuropathic pain disorders, and they exert their analgesic effect through the inhibition of calcium-mediated mono-amine neurotransmitter release, which may lead to pain perception.[7] Numerous prior studies have assessed the utility of pregabalin in painful CP but these studies are of short duration (3 to 8 wk) and have not accounted for the presence of active inflammation (as represented by pseudocysts or pancreatic inflammation on imaging), where pregabalin is less likely to be effective.[8–10]

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The authors declare that they have nothing to disclose.

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In this randomized controlled trial, we aimed to assess the effect of 12 weeks of adjunctive incremental doses of oral pregabalin versus placebo on pain and quality of life in patients with CP in addition to standard care. We also assessed the tolerability of higher doses of pregabalin and possible predictors of response to pregabalin, including QST.

MATERIALS AND METHODS

Trial Design and Setting

This study was an investigator-initiated, double-blinded, placebo-controlled, parallel group randomized controlled trial conducted at a single tertiary care academic institute with a superiority study design. The design of the trial, the analysis and collection of data and the writing of the manuscript were performed by the study authors, and no funding agency/company was involved in the design, conduct or reporting of the trial. The study participants were enrolled over a period of 13 months between October 2021 and November 2022 after obtaining ethical clearance from the Institute's ethics committee (IEC-PG-469/25.08.2021). All participants provided written informed consent for participation in this study and their details were included after anonymizing to avoid their identification, and all additional procedures performed in this study were in accordance with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. This trial protocol was first ethically approved (IEC-PG-447/27.06.2019) and registered at CTRI in 2019 (CTRI/2019/08/020595) but study recruitment was not initiated in view of the ongoing COVID-19 pandemic. The study protocol was revised in 2021 and ethical approval was completed for the amended protocol as well (IEC-PG-469/25.08.2021, RT-18/23.09.2021) before the initiation of patient recruitment. All authors vouch for the accuracy and completeness of the data and for the reporting of adverse events.

Participants

All patients diagnosed with CP who attended an outpatient clinic at the All India Institute of Medical Sciences, New Delhi, over the study inclusion period were screened for inclusion in this study. Briefly, patients with idiopathic or alcohol-related CP with predominant pain and with no significant inflammation or obstruction were considered for inclusion. Operationally, we defined "the lack of significant obstruction" as that group of patients where limited benefit was anticipated with invasive interventions (eg, surgery/endotherapy) and hence, further medical management was required. Cross-sectional imaging was performed in all cases before enrollment to rule out pseudocysts, inflammatory head mass, and other mechanical causes of pain. Patients were also excluded if they had a history of pancreatic surgery or endotherapy. In addition, patients taking antidepressants, anti-epileptics or gabapentinoids over 6 months from the time of screening were excluded. Detailed inclusion and exclusion criteria are provided in the Supplementary content, Supplemental Digital Content 1, http://links.lww.com/JCG/B203.

Definitions of Variables

CP

The diagnosis of CP was made in accordance with Mayo Clinic Diagnostic Criteria.[11] Briefly, diagnosis was based on a total score of 4 or more derived from morphologic and functional criteria including pancreatic calcification, histology, documented steatorrhea, pancreatic duct abnormalities, diabetes, and major clinical criteria (upper abdominal pain or weight loss over 10 kg in 12 mo).

Alcohol-related CP

The diagnosis of ACP was made if the cumulative alcohol intake exceeded 80 g/d for males and 60 g/d for females for at least 5 years in the absence of other causes for CP.

Idiopathic CP

The diagnosis of ICP was made when no etiology for CP could be identified despite detailed etiological workup (clinical history, serum calcium, phosphate, parathyroid hormone levels and lipid profile, imaging including transabdominal ultrasonography, contrast-enhanced computed tomography scans, magnetic resonance cholangiopancreatography/endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound) as appropriate. Genetic testing was not done as a routine for all study participants.

Additional definitions, including complications, various patient outcomes, and QoL are detailed in the Supplementary content, Supplemental Digital Content 1, http://links.lww.com/JCG/B203.

Outcomes

The primary outcome of the study was to assess pain relief using improvement in Izbicki pain score[12] at the end of 12 weeks of study treatment.

The secondary outcomes were also assessed at the end of 12 weeks follow-up, and they included change in quality of life, assessed by the SF-36 questionnaire,[13] interference of pain with daily activities, assessed using modified brief pain inventory-short form (mBPI-sf),[14] and the effect of treatment on patient's life, assessed through patient's global impression of change (PGIC) at 12 weeks follow-up.[15] Additional outcomes studied were the percentage of participants becoming pain free during the study period, tolerability of pregabalin and its adverse effects, number of significant painful days, total need for oral or parenteral analgesics during the study period, and number of hospitalizations for pain. Also, as an exploratory outcome, the role of QST thresholds for response prediction to pregabalin in participants was assessed.[16]

Definitions of Outcomes

Izbicki pain score is a validated pain score designed specifically for CP.[12] The score is a composite of 4 parameters assessing the frequency of pain, pain intensity (VAS score 0-100), use of analgesics, and disease-related inability to work.

Visual analogoue scale (VAS) is a self-reported outcome where the severity of pain is graded on a scale of 0 to 10, with 0 being no pain and 10 being the worst pain ever experienced.[17]

Modified Brief Pain Inventory-Short form (mBPI-SF) is a 14-item questionnaire which was used to assess pain severity and the assessment of the impact of pain on the patient's daily life.[14]

Quality of life assessment was done at the time of recruitment using SF-36 questionnaire,[13] which is a self-reported measure used for assessment of physical, mental, and general well-being.

Study Methodology

All participants underwent detailed history and examination to ascertain that pain could be attributed to CP. All screened participants underwent nutritional assessment using body mass index (BMI), and assessment of complications like steatorrhoea, and diabetes mellitus. Cross-sectional imaging (contrast-enhanced CT/MRI) was done within 3 months from the initiation of study drug (see below) to screen for complications like pseudocysts, bile duct obstruction, duodenal obstruction, splenic vein thrombosis, portal vein thrombosis, inflammatory head mass of pancreas, and carcinoma pancreas. Baseline hematological and laboratory parameters including complete blood count, liver function tests, renal function tests, calcium, phosphate, lipid profile, parathyroid hormone, CA 19-9, glycosylated hemoglobin (HBA1c), and fecal elastase-1 were also assessed. All participants of CP underwent cross-sectional imaging (CECT/MRI) and CRP and completed the PainDETECT questionnaire (PDQ) to exclude other major causes of pain, thereby identifying those with primarily neuropathic pain.

Pain in all study participants was managed according to our institutional protocol with analgesics on demand. We preferred to use an oral combination tablet of mild opioid and non-opioid analgesic (tramadol 37.5 mg and paracetamol 325 mg) for initial pain relief and additional parenteral analgesics [eg, nonsteroidal anti-inflammatory drugs (diclofenac) and strong opioids (pentazocine, fentanyl)] as needed. Patients with CP who had frequent, severe pain episodes not getting relieved by non-opioid and opioid analgesics—indicated by frequent need for oral or IV opioid analgesics, hospitalizations for pain management, and VAS score more than 5/10—were screened for inclusion. Interventions like ERCP (endoscopic retrograde cholangiopancreaticography), and/ or surgical treatment were reserved for patients with favourable anatomy and continued pain despite optimal medical treatment. Pancreatic enzyme replacement therapy was provided to patients with documented pancreatic enzyme insufficiency. Some patients who were already receiving antioxidant therapy continued to receive it during the study period. Diabetes was managed with oral antidiabetic agents and/or insulin, in consultation with an endocrinologist.

At the first visit, pain assessment was done using Izbicki pain score and VAS; mBPI-SF and SF-36 questionnaires were also administered. Participants were trained to use and maintain a pain diary, which could help in further documentation of pain experienced and analgesics used over the follow-up period. Participants were also trained regarding dose uptitration (see later) and were instructed to return all unused study drug to document compliance.

Intervention

Study participants were advised to take incremental doses of either pregabalin or placebo, with the clinician blinded to group assignment. Starting with a dose of 1 capsule (equivalent to 150 mg/d) at night time after dinner, they were instructed to increase the dose every 7 days. They were made to take the initial dose at the time of recruitment and were monitored for 60 minutes for any adverse effects. The dose was increased to 1 capsule twice daily (300 mg/d) after 1 week; and a further increase to 2 capsules twice daily (600 mg/d) after another 1 week. Similar dose increments were followed in the matched placebo group. The doses were taken morning and evening in 2 equivalent doses. In case of unacceptable adverse effects, the dose was down titrated and then an attempt was again made to increase the dose. The maximum tolerable dose was then continued till the end of the study period. Participants were followed up either physically or telephonically at 2-week intervals to assess compliance, tolerability of the drugs, and need for analgesics and hospitalisations. The severity of pain on VAS scale, total oral/ parenteral analgesic doses, and total days of hospitalizations for pain were recorded in the pain diary, in which participants/relatives were asked to document all the events.

After completion of the study period of 12 weeks, the trial participants were called for a final visit to document follow-up Izbicki pain score, mBPI-sf, quality of life (SF-36 questionnaire), and participants' global impression of change (PGIC). In addition, the pain diary was reviewed and a note was made of the total analgesic intake and hospitalisations for pain. The study medications were subsequently stopped. The trial participants were asked to return the surplus medications, and compliance was calculated by the discrepancy in number of pills returned with the expected number of pills to be returned.

QST was performed before enrolment. Thermal stimulation was used to detect pain detection and tolerance thresholds (detailed protocol is provided in the Supplementary content, Supplemental Digital Content 1, http://links.lww.com/JCG/B203). Participants who consented to repeat QST testing were also subjected to QST at the end of the study period and their results were compared.

Randomization and Blinding

Participants meeting eligibility criteria were randomized in 1:1 ratio to receive either pregabalin or placebo. Randomization was done using a simple randomization technique through a computer-generated sequence. Allocation codes were stored in serially numbered sealed opaque envelopes which were opened at the time of allocation to one of either groups. The preparation of randomization list and group allocation were performed by a person not involved in the study to ensure allocation concealment. The same person was responsible for providing the medications according to the randomization code in the numbered package. After randomization, participants received either pregabalin plus standard medical care or they received placebo along with the standard medical care they were already receiving. Both participants and the investigator were blinded to the treatment group assignment. To maintain proper blinding—often compromised in studies involving active drugs like pregabalin due to noticeable side effects such as drowsiness and dizziness—we assigned designated personnel, who were not involved in the clinical management of patients, to objectively assess pain response, analgesic use, and adverse effects in both groups. This approach preserved blinding and minimized potential bias.

Statistical Analysis

Sample size was calculated based on the change in the primary outcome, that is, change in Izbicki pain score. Based on previous studies,[18] it was expected that the study group's Izbicki score would decrease 25% more in the intervention (pregabalin) group. Assuming a baseline Izbicki score of 64 in the study population with an SD of 20,[18] and the score to reduce by 16 more points in the intervention group (compared with placebo), the sample size for a superiority trial was calculated to be 24 participants in

each group, providing a power of 80% and 95% significance level. Assuming 10% loss to follow-up, a sample size of 54 was considered, with 27 participants per patient group.

The prespecified full analysis set for the efficacy and safety analyses consisted of all the participants who were randomized and received at least 1 dose of the trial drug after being included in the study (Intention to treat principle). For the main analysis of primary and secondary end points, the median difference in different outcome parameters in both groups was compared using Kruskal–Wallis test. For dichotomous response-type outcomes (eg, participants pain-free), percentages of participants and between-group differences were calculated and were compared using χ^2 test. For all statistical analyses, P value of less than 0.05 was considered statistically significant.

The assessment of QST for prediction of pain response was done using comparison of pain detection and pain tolerance thresholds measured at the baseline overall and in both arms separately. Change in QST thresholds (from baseline to the end of the study) in each of the groups was compared using Wilcoxon signed rank test. Combined effect of QST threshold at baseline and drug administered on pain relief (change in Izbicki score or improvement in VAS score $>=20$) was assessed using a generalized linear model assuming binomial distribution of outcomes and logit link function.

All data were entered in Microsoft Excel and was analysed using R in RStudio version 2023.03.0+386. Besides the base packages in R, the tableone, tidyverse, and readxl packages were used.

RESULTS

Participants

A total of 139 patients with CP were screened for inclusion over a duration of 13 months (October 2021 to November 2022) of which 55 participants were included and randomized to receive either pregabalin or placebo. One additional participant was randomized in addition to the prespecified sample size to account for 1 participant who was diagnosed to have carcinoma pancreas within 1 month of inclusion. The schematic representation of patient inclusion is shown in Figure 1. Thirty participants were randomized to pregabalin group while 25 participants received placebo. One participant was lost to follow-up in each of the treatment groups and 29 participants who received pregabalin and 24 participants who received placebo were taken up for the analysis of outcomes. Our

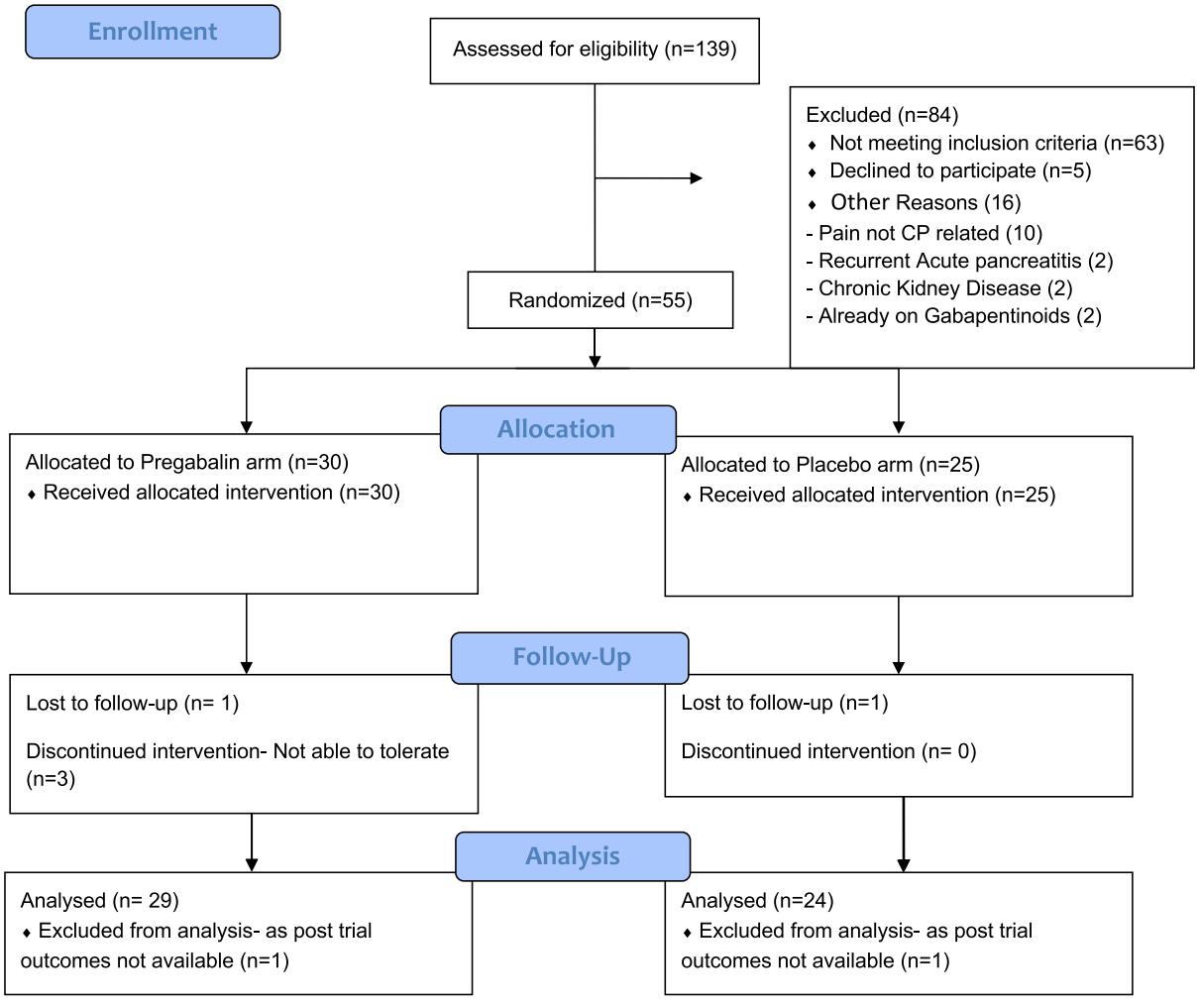

FIGURE 1. CONSORT flow diagram showing enrolment and randomization. CP indicates chronic pancreatitis.

study population predominantly consisted of young males [mean age 29.9 ± 10.6 y; 39/55 (70.9%) males]. Most of the participants had idiopathic CP [alcohol-related CP in 7/55 (12.7%) participants]. Most of the participants with alcohol-related CP were abstinent, with 2/7 (28%) consuming alcohol actively. Smoking history was present in 9/55 (16.4%) participants with 5/9 (55%) smoking actively. The median duration of symptoms before enrolment was 36 months (IQR: 24 to 84 mo). Diabetes mellitus was present in 20 (36.4%) participants, while 15 (27.3%) participants were prediabetic and 20 (36.4%) had normal glycemic profile. Pancreatic exocrine insufficiency(PEI) was diagnosed in 24 (43.6%) participants. All participants in both groups had large-duct disease and both groups were comparable with respect to baseline demographic data and clinical characteristics (Table 1).

Study End Points

Baseline Izbicki pain scores were comparable in both arms at the time of enrolment [median 61.25 (IQR: 57.50 to 67.50) in the pregabalin arm and 60 (IQR: 51.25 to 66.25) in the placebo arm; $P = 0.414$]. At 12 weeks follow-up, both treatment groups showed improvement in pain scores [follow-up score 41.25 (21.25 to 48.44) in the pregabalin arm and 48.75 (33.12 to 72.81) in the placebo arm; $P = 0.029$]; however, there was significantly greater improvement in participants receiving pregabalin as compared with placebo [change in Izbicki −23.75 (−9.69 to −43.75) in pregabalin versus −8.75 (3.44 to −17.50) in placebo arm; $P = 0.005$] (Table 2).

Overall, quality of life as assessed by SF-36 questionnaire significantly improved in participants receiving pregabalin, while it remained unchanged in participants on placebo (Table 2, Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JCG/B204). Notably, most consistent improvement was seen in the domains of energy/fatigue ($P = 0.002$) and limitations due to physical health ($P = 0.023$), while improvement in pain-related quality of life was not statistically significant. Pain severity and its interference with daily activities, as measured by BPI severity and interference scores also improved significantly in participants receiving pregabalin [median change BPI severity −1.83 (−0.83 to −3.75) in pregabalin vs. −0.67 (0.33 to −1.42) in placebo; $P = 0.008$; median change BPI interference score −2.64 (−0.33 to −5.21) in pregabalin vs. −0.43 (1.18 to −2.29) in placebo; $P = 0.009$]. Patients' global impression of change (PGIC) also favoured pregabalin, with 18/29 (62.07%) participants receiving pregabalin reporting at least moderate improvement after intervention, while only 4/24 (16.67%) participants felt similar after placebo. The placebo group had 15/24 (62.5%) of participants either experiencing no change, worsening symptoms, or being almost the same postintervention (Supplementary Table 2, Supplemental Digital Content 3, http://links.lww.com/JCG/B205).

Adverse events in the form of sleepiness (15/29; 51.7% vs. 0%; $P < 0.001$) and giddiness (17/29; 58.6% vs. 1/24 (4.2%); $P < 0.001$) were significantly more common in participants receiving pregabalin (Supplementary Table 3, Supplemental Digital Content 4, http://links.lww.com/JCG/B206). However, discontinuation of the drug was required

TABLE 1. Baseline Differences in Demographic Profiles and Clinical Characteristics of Enrolled Patients

Variables	Placebo arm (N = 25)	Pregabalin arm (N = 30)	*P*
Age at enrolment (y) (mean, SD)	28.8 (10.70)	30.83 (0.68)	0.485
BMI (kg/m^2; mean, SD)	18.82 (3.74)	20.19 (3.33)	0.078
Gender (N, %)	—	—	0.672
Males	17 (68)	22 (73.33)	—
Females	8 (32)	8 (26.67)	—
Etiology (%)	—	—	0.393
Idiopathic	23 (92)	25 (83.33)	—
Alcohol-related	2 (8)	5 (16.67)	—
Active alcohol consumer	0 (0)	2 (6.67)	0.89
Nonsmoker	25 (83.33)	21 (84)	0.654
Active smoker	2 (6.67)	3 (12)	—
Disease duration/time since onset of pain (mo) (median, IQR)	50 (24-80)	35 (24-84)	0.692
Diabetic mellitus	—	—	0.84
Diabetes	9 (36)	11 (36.67)	—
Prediabetes	6 (24)	9 (30)	—
Duration of diabetes mellitus (mo) (Median, IQR)	24 (24-84)	23.5 (6-43)	0.9
Clinical steatorrhea	10 (40)	14 (46.67)	0.823
On PERT	19 (76)	18 (60)	0.332
Antioxidant therapy	10 (40)	12 (40)	1.0
Haemoglobin (g/dL) (mean, SD)	13.42 (1.67)	12.60 (1.77)	0.089
TLC (per cu.mm) (mean, SD)	7874 (2170.30)	8053.67 (2408.21)	0.774
Platelets (10^3/uL) (mean, SD)	224.96 (72.49)	257.5 (104.88)	0.195
T. Bilirubin (mg/dL) (median, IQR)	0.68 (0.4-1.08)	0.42 (0.32-0.59)	0.031
ALP (U/L) (Median, IQR)	107 (92-134)	116 (83-157)	0.685
Albumin (gm/dL) (mean, SD)	4.77 (0.47)	4.68 (0.51)	0.508
CRP (mg/L) (median, IQR)	1 (0.5-2)	1.65 (0.7-5.1)	0.89
Baseline Izbicki pain Score	60.00 (51.25-66.25)	61.25 (57.50-67.50)	0.414
Baseline Worst VAS	9.0 (8-10)	9.0 (8-10)	0.483
Baseline BPI severity	4.0 (3.67-5.67)	4.67 (3.67-5.33)	0.438
Baseline BPI interference	5.86 (5.0-6.86)	6.0 (4.57-7.29)	0.424

ALP indicates alkaline phosphatase; BMI, body mass index; BPI, Brief Pain Inventory; CRP, C-reactive protein; IQR, interquartile range; PERT, pancreatic enzyme replacement therapy; TLC, total leucocyte count; VAS, visual analogue scale.

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TABLE 2. Interval Change in the Izbicki Pain Score, Brief Pain Inventory Severity and Interference Score, VAS Score, and Quality of Life Domains According to SF-36 Questionnaire in the 2 Study Arms

Variables	Placebo arm (n = 24)	Pregabalin arm (n = 29)	Mean intergroup difference (95% confidence intervals)	*P*
Primary outcome				
Izbicki pain score change [Median (IQR)]	−8.75 [3.44 to −17.50]	−23.75 [−9.69 to −43.75]	16.75 (6.91 to 26.59)	0.005
Secondary outcomes				
BPI severity change [median (IQR)]	−0.67 [0.33 to −1.42]	−1.83 [−0.83 to −3.75]	1.44 (0.4 to 2.48)	0.008
BPI interference change [median (IQR)]	−0.43 [1.18 to −2.29]	−2.64 [−0.43 to −5.21]	1.87 (0.4 to 3.35)	0.009
Worst VAS Score change [median (IQR)]	−1.0 [1.0 to −2.0]	−4.0 [−0.75 to −6.25]	2.5 (0.88 to 4.15)	0.008
Moderate or better improvement on PGIC	4 (16.7%)	18 (62.1%)	45.4% (22.3% to 68.5%)	<0.001
Overall QoL change [median (IQR)]	10.50 [−68.62 to 153.16]	218.99 [21.75 to 371.90]	−157.0 (−269.4 to −44.6)	0.023
Quality of life components by SF-36				
Physical functioning QoL [median (IQR)]	0.00 [−15.00 to 6.25]	15.00 [3.75 to 35.00]	−12.8 (−25.1 to −0.49)	0.031
Role limitations due to physical health QoL [median (IQR)]	0.00 [−31.25 to 0.00]	50.00 [0.00 to 100.00]	−29.2 (−55.4 to −2.9)	0.023
Role limitations due to emotional health QoL [Median (IQR)]	0.00 [−33.33 to 0.00]	50.00 [0.00 to 66.70]	−28.6 (−56.6 to 0.52)	0.068
Energy/fatigue QoL [median (IQR)]	7.50 [−15.00 to 10.00]	25.00 [10.00 to 40.00]	−21.5 (−34.6 to −8.4)	0.002
Emotional well-being QoL [median (IQR)]	−4.00 [−16.00 to 9.00]	14.00 [2.00 to 41.00]	−15.5 (−28.2 to −2.84)	0.027
Social functioning QoL [median (IQR)]	11.75 [12.50 to 25.00]	18.75 [0.00 to 40.62]	−18.2 (−33.8 to −2.6)	0.057
Pain QoL [median (IQR)]	11.25 [−10.62 to 35.00]	27.50 [1.25 to 60.00]	−15.4 (−33.8 to 3.0)	0.105
General health QoL [median (IQR)]	2.50 [−11.25 to 10.00]	20.00 [1.25 to 40.00]	−15.8 (−28.0 to −3.6)	0.022

BPI indicates Brief Pain Inventory; QoL, quality of life; VAS, visual analogue scale.

in only 3/29 (10.4%) participants receiving pregabalin. Compliance with the treatment protocol was good, with 95.83% in the placebo group and 89.65% in the pregabalin group taking more than 50% of the administered drugs [$P = 0.54$]. Majority of the (19/29; 65.5%) participants could tolerate maximum dose up to 600 mg/day, with the average tolerated dose being 475 ± 188 mg of pregabalin. There was a trend towards improvement in the number of significant painful days (VAS > 5; median 5 (0.75 to 13.5) with pregabalin versus 9 (2.75 to 20) with placebo; $P = 0.137$) and the number of days additional analgesics were required (median 4.5 (0 to 14.25) with pregabalin and 15 (1.75-30) with placebo; $P = 0.084$) in participants receiving pregabalin. Reduction in the worst VAS scores (maximum pain) was better in participants receiving pregabalin [−4.0 (−0.75 to −6.25) for pregabalin vs. −1.0 (1.0 to −2.0) for placebo; $P = 0.008$] (Fig. 2). Number of participants becoming completely pain-free, number of hospital visits and the number of days parenteral analgesics were required were statistically similar in both groups (Table 3).

QST was performed in 24/30 (80%) participants receiving pregabalin and 17/25 (68%) participants receiving placebo at baseline. Follow-up QST at 3 months were available for 11/29 (37.9%) and 13/24 (54.1%) participants receiving pregabalin and placebo, respectively. There was no significant change in pain detection (PDT) ($P = 0.944$) or pain tolerance thresholds (PTT) ($P = 0.439$) in either of the treatment groups. Izbicki pain scores or pain relief (as indicated by change in VAS ≥20) were not associated with baseline PDT or PTT. With increasing PDT, there was no significant trend in pain response among participants who received pregabalin or placebo (Supplementary Figure, Supplemental Digital Content 5, http://links.lww.com/JCG/B207). Overall, no QST parameter could be used to predict responsiveness to pregabalin, and no change in QST parameters was seen with pregabalin use.

DISCUSSION

Pain management in patients with CP is complicated, and needs a multipronged approach with a special focus on the neuropathic nature of this pain, as demonstrated in this study. Our study results indicate that pregabalin effectively reduces pain intensity and improves quality of life when administered for an extended duration of 12 weeks. Notably, this study shows effectiveness and tolerability of high dose pregabalin as a pain relief measure in patients with CP, especially among patients who do not have significant obstructive or inflammatory pathology.

Pain affects over 85% of individuals at some point during the course of the disease[2,19] and is the primary reason for hospitalization in patients with CP. Pregabalin, commonly used for neuropathic pain, has been previously used in the treatment of pain due to CP (Table 4).[8–10] These studies were variable in terms of dosage, duration of therapy (3 to 8 wk), subgroup of patients considered (any painful CP, postductal clearance CP, etc.) and whether or not antioxidants were administered. However, all studies reported similar pain relief, indicating the replicability of the effect of pregabalin in patients with CP. Building upon the pre-existing data, our study demonstrates that higher dosage of pregabalin (up to 600 mg) when administered for a longer duration of 12 weeks leads to pain relief in patients with CP. We excluded patients with significant ongoing inflammation on imaging and those in whom ductal obstruction was felt to be the major cause of pain, thus "enriching" the patients with likely neuropathic pathology and therefore restricting our study to patients most likely to respond to pregabalin. The pain response in the placebo group was lower in comparison to previous studies, indicating the definite need for adjunctive therapy in this patient subgroup and the lower likelihood for spontaneous resolution of pain. Possible additional reasons for lower placebo pain response could include use of trial drug as an adjunct, rather than an isolated therapy, longer duration of the assessment, and use of composite score for

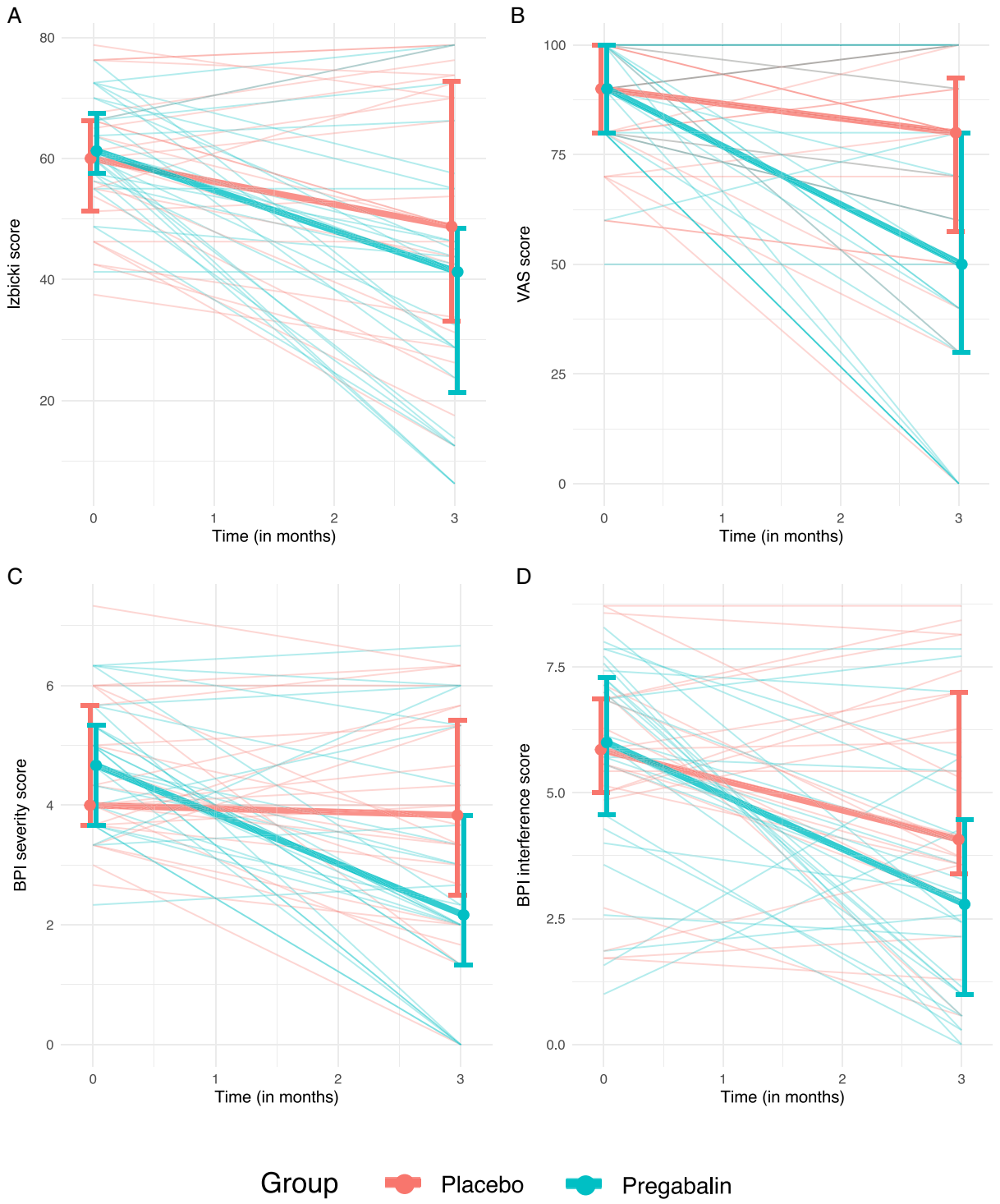

FIGURE 2. Interval change in Izbicki pain score (A) and maximum VAS score (B), BPI severity (C), BPI interference (D) in both arms (Red: placebo arm, Blue: pregabalin arm).

pain assessment, that takes into account the use of analgesics and inability to work in addition to the frequency and intensity of pain, and is thus less likely to have misclassified pain response. Whether or not this subgroup and its response to pregabalin is reproducible remains to be validated in future studies.

Administration of pregabalin was also associated with improvement in quality of life (SF-36 questionnaire),[13] and reduced interference of pain with daily activities (mBPI-SF questionnaire).[14] Participants receiving pregabalin also reported overall improvement more frequently than those receiving placebo. Interestingly, all domains of quality of life

TABLE 3. Differences in the Clinical Outcomes of Enrolled Patients in 2 Arms During Study Period

Variables	Placebo arm (n = 24)	Pregabalin arm (N = 29)	Intergroup difference (95% confidence interval)	*P*
No. participants becoming totally pain-free [n(%)]	4 (16.67)	9 (31.03)	14.4% (−8.1% to 36.9%)	0.226
No. significant painful days [median(IQR)]	9.0 (3.0-20.0)	5.0 (0.75-13.50)	−5.4 (−12.1 to 1.2)	0.137
Total Number of oral analgesics required for pain relief [median (IQR)]	15.0 (1.75-30.0)	4.5 (0.0-14.25)	−12.2 (−26.2 to 1.8)	0.084
No. participants requiring IV/IM analgesics for pain relief [n (%)]	11 (45.83)	10 (34.48)	−11.4% (−37.7% to 15.0%)	0.78
No. participants requiring hospitalisations for pain relief [n (%)]	8 (33.33)	7 (24.13)	−9.2% (−33.7% to 15.3%)	0.46
Number of hospitalisations due to pain episodes [median (IQR)]	0 (0-2.25)	0 (0-0.25)	−0.04 (−1.74 to 1.67)	0.415
Surgery	1 (4.16)	1 (3.45)	-	0.89
USG-guided celiac plexus block	0 (0)	1 (3.45)	-	1

IQR indicates interquartile range; USG, ultrasonography.

assessed by SF-36 did not improve similarly, and the improvement in pain-related QoL fell short of statistical significance. This highlights that pregabalin may lead to improvement in multiple aspects of QoL, including lack of energy and fatigue, and limitations due to physical health, that contributes to lesser interference of pain with daily activities, ultimately resulting in reduced pain perception and impression of overall change. While the impact of pregabalin on QoL has been variable in past studies,[8] the pleiotropy of pregabalin's effect needs to be evaluated further, and may be of use especially considering the multidimensional nature of pain in these patients.

The adverse events in our study related to pregabalin use were comparable to the previous studies[8–10] which is noteworthy, considering the fact that we used relatively higher dose of drugs for long duration, with a total of 19/29 (65.51%) participants receiving 600 mg/d of pregabalin. Prominent adverse effects noticed by participants were giddiness (58.62%) and drowsiness (51.7%), which were mostly manageable by dose reduction alone, and required drug discontinuation in only 3/29 (10.4%) participants. The lack of significant adverse events with significant improvement in pain and QoL makes pregabalin a worthy adjunct in patients with painful CP.

We also explored the role of QST by assessing pain detection and tolerance thresholds in a subset of participants both before and after administering pregabalin or placebo. We could not find any QST parameter that could predict responsiveness to pregabalin, and no pain thresholds were seen to change significantly with pregabalin. These results were in contrast to observations in previous studies,[5,20] which could be related to variability in study protocols

TABLE 4. Summary of Previous Randomized Controlled Trials on Pregabalin Use in Patients With CP

	Olesen et al[8]	Talukdar et al[9]	Sureshkumar et al[10]	Present study
Intervention duration	3 wk	8 wk	8 wk	12 wk
Patient population	Any painful chronic pancreatitis patients	Postductal clearance in chronic pancreatitis patients	Any painful chronic pancreatitis	Painful chronic pancreatitis patients with no active inflammation, no pseudocyst, no ductal obstruction
Intervention	Pregabalin vs. placebo	Pregabalin-antioxidant combination vs. placebo	Pregabalin-antioxidant combination vs. placebo	Pregabalin vs. placebo
No. patients	30 vs. 34	42 vs. 45	45 vs. 45	30 vs. 25
VAS change	Average pain reduction (−36% vs. −24%; $P = 0.02$) maximum pain reduction (−32% vs. −22%; $P = 0.02$)	At 2 mo, (−24 in pregabalin-antioxidant group vs. −20 in placebo group) at 6 mo [−40 in pregabalin-antioxidant group vs. −44 in placebo group]	At 8 wk, −2.08 vs. −1.44; $P = 0.0001$ At 12 wk, −2.00 vs. −1.3; $P = 0.0007$	At 12 wk, −4.0 (−0.0.75 to −6.25) vs. −1.0 (1.0 to −2.0); $P = 0.008$
Izbicki pain score change	NA	At 8 wk, −33.5 in pregabalin-antioxidant group vs. −21.3 in placebo group	At 8 wk, −6.76 vs. −3.37; $P = 0.002$ At 12 wk, −7.76 vs. −5.67; $P = 0.20$	−23.75 (−9.69 to −43.75) vs. −8.75 (3.44 to −17.50); $P = 0.005$
Total number of painful days	NA	10.0 (2.0-16.0) vs. 18.0 (7.0-34.0); $P = -0.01$	14 ± 4 vs. 26 ± 6; $P = 0.001$	5.0 (0.75 to 13.50) vs. 9.0 (3.0-20.0); $P = 0.137$
Proportion of patients with complete pain resolution	NA	20 (47.6%) vs. 12 (26.7%); $P = 0.04$	26 (57.7%) vs. 10 (22.2%); $P = 0.04$	9 (31.03%) vs. 4 (16.67%)

and modalities (pressure vs. thermal) used for pain induction. Our study highlights 2 important findings. First, QST may not be a perfect tool for assessing the contribution of neuropathy to pain in these patients. Second, the patients who are likely to respond to pregabalin cannot be identified using QST alone, and clinical decision-making is still of vital importance in selecting patients for a trial of pregabalin. Overall, our results also highlight the need for better objective assessment tools for the neuropathic component of pain in CP, which may predict response to neuromodulating drugs like pregabalin in the future.

Our results have validated the utility of pregabalin in patients with painful CP, when administered at relatively higher doses for prolonged duration. However, our study is not without its limitations. First, we attempted to exclude patients with the evidence of ongoing inflammation on imaging and those who were expected to have significant obstructive pathology. This introduces subjectivity to the inclusion criteria, as the assessment of these parameters can be difficult, and in clinical practice, the time duration between imaging and assessment could be long enough such that new collections/ obstruction may have developed, which may limit the generalizability of inclusion criteria in routine practice. Second, all participants were not compliant on pregabalin at the prescribed dose, with 3 participants discontinuing it altogether, introducing heterogeneity in the results. Third, all participants did not undergo QST either before or after the administration of the drug, and our interpretation of its utility may therefore be limited by sample size and selection bias. Fourth, our study did not specifically assess the incremental benefits of dose escalation. The uptitration of pregabalin doses in our cohort was primarily aimed at improving patient tolerance. In our study, we demonstrated that higher doses of pregabalin, when administered for a longer duration (12 weeks), were both safe and effective for managing pain in patients with chronic pancreatitis. However, the lack of a direct comparison of incremental doses of pregabalin means that the optimal dosage and duration of treatment for painful CP remain speculative. Further research is needed to confirm these findings and explore the potential for dose-dependent benefits. Fifth, although blinding was maintained at the investigator's end, it is challenging to preserve blinding at the patient level in trials involving medications like pregabalin, due to its distinct and often noticeable side effects. Finally, ours was a single centre study, including participants with similar ethnic background who had predominantly idiopathic CP. Broader applicability of our results needs to be established in a larger multicentre trial.

To conclude, pregabalin as an adjunctive therapy improves pain, its interference with daily activities and quality of life in patients with CP, and is well tolerated in higher doses. The subgroup of patients with CP likely to respond to pregabalin is difficult to identify based on QST alone, and needs further studies. Long term efficacy and adverse effects with pregabalin still need to be explored.

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