ORIGINAL ARTICLE

Effect of Single-dose Preoperative Pregabalin on Postoperative Pain after Cardiac Surgery: A Prospective Observational Randomized Double-blind Study

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ABSTRACT

Aim and objective: We evaluated the effect of preoperative single-dose pregabalin (PG) on postoperative pain in patients undergoing on-pump coronary artery bypass graft (CABG) surgery.

Materials and methods: In this double-blind study, 60 adult patients scheduled for elective on-pump CABG surgery were randomized into two groups of 30 each, viz., PG and placebo (PL). Patients received either oral PG 150 mg or a PL, 1 hour before surgery. All patients received general anesthesia. Postoperative pain relief was provided with intravenous tramadol 50 mg 8 hourly. Postoperative pain was assessed, both at rest and during coughing, with the 10-point verbal rating scale (VRS) at 6, 12, 18, and 24 hours after extubation. Time to extubation, pain scores, requirement of additional analgesics, and adverse effects were compared using chi-square test, unpaired t test, and Mann–Whitney U test.

Results: The time to extubation was significantly prolonged in the PG group compared with PL (9.84 ± 1.88 *vs* 8.66 ± 2.12 hours, p = 0.027). The mean VRS scores at rest and during coughing were significantly lower in the PG group compared with PL (p < 0.05). However, the requirement of additional analgesics, such as paracetamol or tramadol was similar in the two groups.

Conclusion: A single preoperative oral dose of PG 150 mg was effective in reducing postoperative pain in patients undergoing on-pump CABG compared with a PL.

Keywords: On-pump coronary artery bypass graft, Postoperative pain, Preemptive analgesia, Pregabalin.

INTRODUCTION

During the recovery phase after cardiac surgery, intense pain has been associated with cardiovascular stress

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response, reduced capacity to cough, and increased incidence of atelectasis. Adequate pain control is important to maintain hemodynamic stability, hasten the postoperative recovery, and prevent progression to chronic pain.[1]

Preemptive analgesia is defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain.[2] Gabapentinoids [gabapentin and pregabalin (PG)] are relatively new drugs, which were originally introduced as antiepileptics, but have also been found to have analgesic, anticonvulsant, and anxiolytic effects. They reduce the hyperexcitability of dorsal horn neurons induced by tissue injury due to trauma or surgery. Reduction in central sensitization by gabapentin and PG may reduce acute postoperative pain.[2]

Pregabalin is a structural analog of gamma aminobutyric acid. It acts by presynaptic binding to the alpha-2-gamma subunit of voltage-gated calcium channels that are widely distributed in the spinal cord and brain. Pregabalin decreases the release of neurotransmitters including glutamate, noradrenaline, substance P, and calcitonin gene-related peptide-producing inhibitory modulation of overexcited neurons and returning them to a normal state. The half-life for PG is 6.3 hours. Pregabalin is rapidly absorbed when administered on an empty stomach, with peak plasma concentrations occurring within 1 hour. Pregabalin has distinct pharmacokinetic advantage over gabapentin. It has a higher bioavailability (90 *vs* 33%). Lower doses are required and, hence, have less side effects.

The major metabolite is N-methyl PG.[2,3] Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug.[2,3]

The objective of this study was to evaluate the effect of preoperative single-dose PG on postoperative pain and to assess if it reduces the requirement of additional analgesics. Our secondary outcome was to study the adverse effects, if any.

MATERIALS AND METHODS

The study was approved by the hospital scientific and ethics committee. After obtaining informed and written consent, 60 adult patients (18–80 years) of either sex

scheduled for elective on-pump coronary artery bypass graft (CABG) surgery under general anesthesia were enrolled in the study. It was a randomized, prospective, double-blind, placebo (PL)-controlled, parallel design, clinical study. Patients were randomized into two groups of 30 each, viz., PG and PL. Randomization was done using a computer-generated sequence and closed opaque envelope system. Patients received either oral PG 150 mg or a PL (similar-looking empty capsule) 1 hour before surgery. The investigators as well as assessors remained blinded to the group assignment.

Patients with body mass index >30, history of chronic analgesic use, on tranquilizer, anticonvulsant or anti-depressant drugs, alcohol dependence, malabsorption, hepatic and renal insufficiency, emergency surgery, previous cardiac surgery, left ventricular ejection fraction <25%, preoperative use of inotropic agents or intra-aortic balloon pump , known allergy to the study drug, and off-pump CABG were excluded from the study.

The day before surgery, all patients were visited for preanesthesia check-up, and informed consent obtained after explaining the study protocol. All patients received tablet alprazolam 0.25 mg the night before and at 6.00 am on the morning of surgery. Also, cardiac medications except angiotensin-converting enzyme inhibitors were continued until the morning of surgery.

After attaching monitors and starting oxygen 4 L/minute by nasal prongs, patients were premedicated with intravenous midazolam 0.02 mg/kg. Arterial and central venous cannulations were done under local anesthesia. Induction was done with fentanyl 5 µg/kg, etomidate 0.1 to 0.2 mg/kg, and rocuronium 1 mg/kg. After tracheal intubation, depth of anesthesia was maintained with iso-flurane in 50% nitrous oxide and oxygen to maintain the bispectral index (BIS) between 40 and 60. Nitrous oxide was discontinued prior to aortic cannulation. Boluses of fentanyl 50 µg were administered when needed to maintain mean arterial pressure of 65 to 85 mm Hg and heart rate between 50 and 90 beats/minute. Supplemental doses of rocuronium 0.02 mg/kg were repeated every 30 minutes until the end of surgery. Monitoring included electrocardiogram, oxygen saturation (SpO_2), invasive blood pressure, pulmonary artery pressure, end-tidal carbon dioxide, BIS, and nasopharyngeal temperature.

Surgery was done through median sternotomy using cardiopulmonary bypass. Postoperatively, the patients were electively ventilated. Intravenous tramadol 50 mg 8 hourly was used for postoperative analgesia immediately after shifting to intensive care unit. Intravenous midazolam 1 to 2 mg boluses were used for sedation until effect of muscle relaxant wore off. Intravenous fentanyl 50 µg boluses were administered if hypertension and tachycardia occurred or patient was restless on ventilator.

Postoperative pain was assessed by an anesthesiologist or a nurse blinded to the groups, both at rest and during coughing with the 10-point verbal rating scale (VRS) with 0 as "no pain" and 10 as "worst pain." This was recorded at 6, 12, 18, and 24 hours after extubation. Additional tramadol 50 mg intravenously was administered if VRS score >4. If verbal rating scale score persisted >4 despite additional tramadol, intravenous paracetamol 1 mg was administered. Time to extubation, pain scores during rest and coughing, additional analgesic requirement, fentanyl consumption, inotrope and vasopressors required, Ramsay sedation score (1: Anxious/restless/both; 2: Cooperative, oriented, and tranquil; 3: Responding to commands; 4: Brisk response to stimulus; 5: Sluggish response to stimulus; 6: No response to stimulus), and adverse effects were compared. Adverse effects, such as respiratory depression (rate <8 breaths/minute or SpO_2 <90%), nausea, and vomiting were studied.

Statistical analysis was performed using Statistical Package for the Social Sciences version 12 for windows. The comparison of data between groups was determined by using chi-square test, unpaired t test, Mann–Whitney U test. Fisher's exact test where appropriate was used to identify differences between the two groups. Correlations between continuous variables were assessed using Pearson correlation coefficient. The results were expressed as mean ± standard deviation. A probability value of <0.05 was considered statistically significant.

RESULTS

The demographic data and clinical characteristics were comparable in the two groups (Table 1). The consumption of fentanyl and midazolam was significantly less in the PG group intraoperatively (Table 2). Patients in the PG group were found to have less vasopressor requirement compared with the PL group (p < 0.05). The perioperative requirement of inotropic agents was similar in the two groups (Table 2). The time to extubation was significantly prolonged in the PG group (Table 2). The mean VRS scores

Table 1: Demographic and clinical characteristics

Patient characteristics	PL group Mean ± SD	PG group Mean ± SD	p-value
Age (years)	61.33 ± 8.63	59.40 ± 7.64	0.362
Sex (M:F)	27:3	24:6	0.472
BMI	26.67 ± 3.69	24.96 ± 3.78	0.082
EF (%)	47.53 ± 10.95	43.53 ± 9.31	0.133
Hypertension	24:6	22:8	0.761
Diabetes	16:14	9:21	0.115
COPD	1:29	0:30	1.000
Smoking	4:26	1:29	0.353
No. of grafts	3.57 ± 0.817	3.47 ± 0.819	0.638
Duration of anesthesia in (h)	4.10 ± 0.92	4.35 ± 0.74	0.058

Table 2: Perioperative variables

Variable		PL group	PG group	p-value
Vasopressors (required: not required) intraoperatively		13:17	3:27	0.007
Inotropes (required: not required)		9:21	6:24	0.552
Intraoperatively postoperatively		6:24	4:26	0.731
Fentanyl mcg requirement	Intraoperatively	530 ± 182.70	443.33 ± 157.97	0.035
Mean ± SD	Postoperatively	100 ± 61.24	297 ± 251.23	0.076
Midazolam requirement	Intraoperatively	3.97 ± 2.04	2.8 ± 1.56	0.025
Mean ± SD	Postoperatively	2 ± 1.41	6.86 ±5.67	0.073
Time to extubation		8.66 ± 2.12	9.84 ± 1.88	0.027

Table 3: Verbal rating scale scores

Variable	PL group	PG group	p-value
Pain score at rest			
6(h)	4.73 ± 1.93	3.43 ± 2.54	0.002
12	4.37 ± 1.77	3.10 ± 2.16	0.005
18	3.77 ± 1.57	2.57 ± 1.77	0.001
24	3.27 ± 1.55	1.93 ± 1.39	0.001
Pain score with cough			
6(h)	5.73 ± 2.10	4.13 ± 2.60	0.002
12	5.33 ± 1.99	3.93 ± 2.18	0.005
18	5.13 ± 1.85	3.50 ± 1.93	0.001
24	4.63 ± 2.09	2.73 ± 1.51	0.000
Ramsay sedation score			
06(h)	2.00 ± 0.27	2.04 ± 0.19	0.823
12	2.00 ± 0.00	2.07 ± 0.26	0.643
18	2.00 ± 0.00	2.07 ± 0.26	0.643
24	2.00 ± 0.00	1.96 ± 0.33	0.817

Table 4: Paracetamol requirement

Variable	PL group	PG group	p-value
6 h	0.75 ± 0.35	1.0 ± 0.00	0.306
12	1.00 ± 0.00	1.0 ± 0.00	1.000
18	0.83 ± 0.29	1.00 ± 0.00	1.000
24	1.00 ± 0.00	1.00 ± 0.00	1.000

at rest and during coughing at 6, 12, 18, and 24 hours were significantly lower in the PG group compared with the PL ($p < 0.05$; Table 3) (Graph 1 and 2). The requirement of additional analgesics was not found to be statistically different in the two groups (Table 4) (Graph 3 and 4). Ramsay sedation score during 24 hours after extubation was similar between the two groups (Table 3). The difference in nausea, vomiting, and respiratory depression between the two groups was not found to be statistically significant.

DISCUSSION

This study demonstrated that a single dose of 150 mg PG administered orally 1 hour prior to surgery resulted in less intraoperative opioid requirement and improvement in postoperative pain scores at rest and with cough for up to 24 hours. The result of this study correlates well with the study of Jokela et al[4] and Reuben et al.[5]

Jokela et al[4] observed that perioperative administration of PG 300 mg before and after laparoscopic hysterectomy decreases oxycodon consumption, but they observed increase in number of side effects. Reuben et al[5] also found that in patients undergoing lumber laminectomy, PG 150 mg before and after surgery was as effective as celecoxib in reducing postoperative pain

and patient-controlled morphine consumption, and the combination of both drugs was most effective with fewer side effects. A study by Akhavanakbari et al[6] also observed that a single preoperative oral dose of PG 150 mg is an effective method for reducing postoperative pain in patients undergoing orthopedic surgery. The perioperative administration of PG has a significant opioid-sparing effect in the first 24 hours after surgery. Postoperative nausea and vomiting and sedation score were reduced with PG administration. Meta-analysis by Zhang et al[7] indicated that PG significantly reduced postoperative opioid consumption. They also showed that PG consumption can reduce some opioid side effects, such as nausea and vomiting.

On the contrary, in a recently published article, Paech et al[8] reported that a single preoperative dose of 100 mg PG was ineffective in reducing acute postoperative pain or improving recovery after minor gynecological surgery. Sundar et al[2] observed that a single oral dose of 150 mg PG given 1 hour prior to off-pump coronary artery bypass surgery did not show any effect on perioperative opioid consumption.[1] Mathiesen et al[9] also observed that PG 300 mg preoperatively with or without dexamethasone made no difference to pain scores after abdominal hysterectomy over 24 hours. The differences in the PG dosages and types of surgery have thus yielded contrasting results.

In several studies, the presence of complications among the patients is different. Hill et al[10] and Paech et al[8] reported higher rates of complications, such as vomiting, nausea, and abdominal pain in the PG group, while Agarwal et al,[11] and Mathiesen et al[9] reported lower rates in the PG group. Our study showed no significant difference in the adverse effects in both the groups.
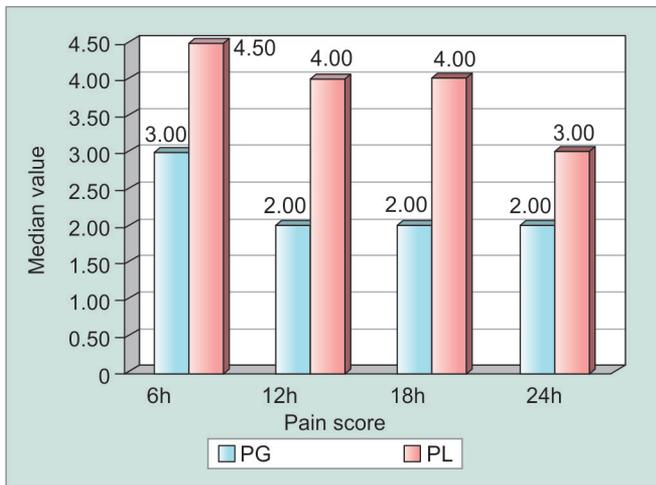
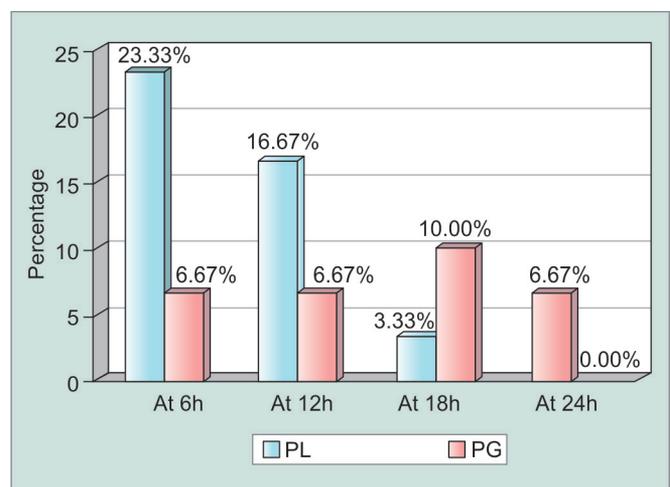**Graph 1:** Comparison of pain score at rest among study groups
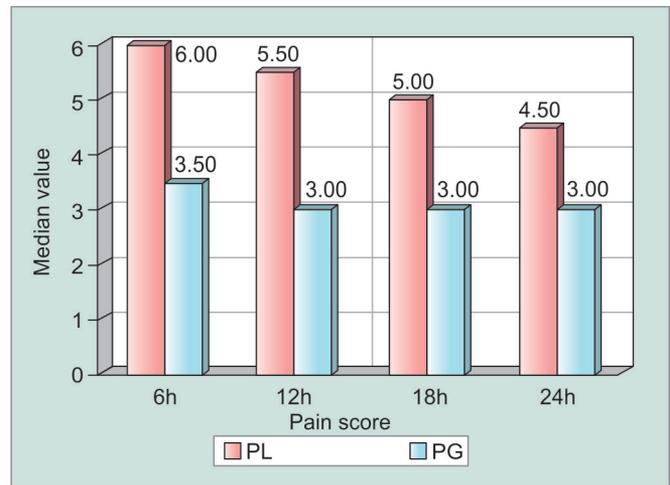
Graph 2: Comparison of pain score with cough among study groups
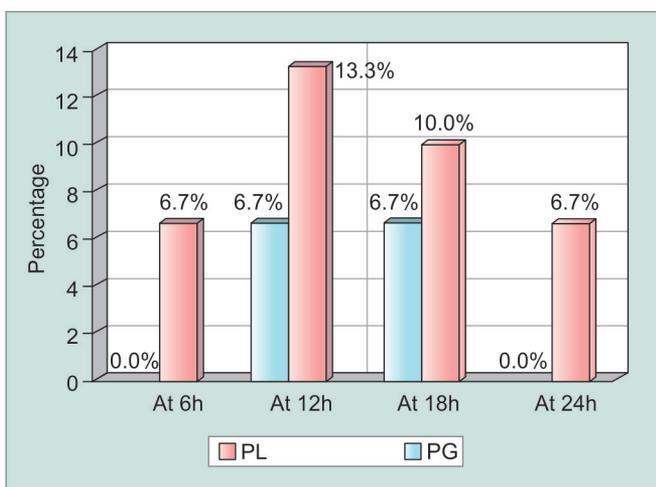
Graph 3: Comparison of additional tramadol requirement among study groups

Graph 4: Comparison of additional paracetamol requirement in the study groups

The goal of postoperative multimodal analgesia is not only the improved quality of analgesia, but also the reduction in opioid-related side effects.[12] Although we did find better pain relief in the PG group, the requirement of additional analgesics like paracetamol and tramadol was not statistically significant between the two groups. After using multimodal analgesia in the present study, however, we did not find any opioid-related side effects. It is possible that a higher dose of PG could have more analgesic potency, but also more side effects.[4] Also, we observed higher opioid requirement postoperatively in the PG group. This could have been avoided either by using a higher dose initially or a repeat dose postoperatively. The decreased opioid requirement in the PL group postoperatively can be attributed to increased intraoperative requirement and probable cumulative effect of opioids.

CONCLUSION

Preoperative PG attenuated postoperative pain at rest and during coughing following on-pump CABG, and had opioid-sparing effects intraoperatively.

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