Original Article

The effects of preemptive pregabalin on attenuation of stress response to endotracheal intubation and opioid-sparing effect in patients undergoing off-pump coronary artery bypass grafting

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ABSTRACT

The clinical study was designed to evaluate and compare single preoperative dose of pregabalin to a placebo regarding hemodynamic responses to laryngoscopy and endotracheal intubation, to assess perioperative fentanyl requirement and any side-effects. It was a randomized, double-blind, placebo-controlled, parallel assignment, efficacy study. The study was done at a tertiary university hospital. This study was a comparison between two groups of 30 adult patients scheduled for elective off pump coronary artery bypass surgery. In the control group, the patients were given placebo capsules, and in the pregabalin group, the patients were given pregabalin 150 mg capsule orally 1 h before surgery. The patients were compared for hemodynamic changes before the start of the surgery, after induction, 1, 3, and 5 min after intubation. Additionally, fentanyl requirement during surgery and the first postoperative day was also compared. The present study shows that a single oral dose of 150 mg pregabalin given 1 h before surgery attenuated the pressor response to tracheal intubation in adults, but the drug did not show any effect on perioperative opioid consumption and was devoid of side-effects in the given dose.

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INTRODUCTION

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Preemptive analgesia is defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain.[1] The concept of preemptive analgesia to reduce postoperative pain was founded on a series of successful animal experimental studies that demonstrated central nervous system plasticity and sensitization after nociception.[2-4] A variety of interventions have been used to achieve a pronounced preemptive effect, such as epidural analgesia, peripheral local anesthetic infiltrations, systemic *N*-methyl D-aspartate receptor antagonists, systemic non-steroidal anti-inflammatory drugs and systemic opioids.[5,6]

Gabapentinoids (gabapentin and pregabalin) are relatively new drugs, which were originally introduced as antiepileptics and also have analgesic, anticonvulsant, and anxiolytic effects. These drugs are well tolerated by patients and produce limited side-effects. Pregabalin is a structural analog

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of gamma-aminobutyric acid (GABA). It acts by presynaptic binding to the α-2-γ subunit of voltage-gated calcium channels that are widely distributed in the spinal cord and brain.[7] By altering calcium currents, pregabalin reduces or modulates the release of several excitatory neurotransmitters, including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide, producing inhibitory modulation of "overexcited" neurons and returning them to a "normal" state. Thus, pregabalin appears to reduce the hyperexcitability of dorsal horn neurons that is induced by tissue damage.[8]

Pregabalin had been shown to be effective in neuropathic pain, diabetic neuropathy, postherpetic neuralgia, reflex sympathetic dystrophy, acute postoperative pain, and in reducing the postoperative opioid requirements.[3,9] Furthermore, a growing body of evidence suggests that perioperative administration is efficacious for preoperative anxiolysis, preventing chronic postsurgical pain, postoperative nausea and vomiting, and delirium.[10-12] Because patients may be anxious in the perioperative period, the anxiolytic effects of pregabalin may be beneficial.[13,14]

Gabapentin was effectively used to attenuate hemodynamic response to laryngoscopy and tracheal intubation.[15-18] Only one study in the available literature evaluated the efficacy of pregabalin for preventing intubation response. Eren *et al*., evaluated the effectiveness of pregabalin in suppressing the hemodynamic response to intubation in lumbar spinal surgeries.[19] Till now the efficacy of pregabalin in attenuation of stress response during tracheal intubation has not been reported in patients undergoing off-pump coronary artery bypass (OPCAB) grafting. The present study was aimed to investigate the effect of pregabalin on the changes in blood pressure and heart rate observed during laryngoscopy and tracheal intubation. Another aim was to assess the opioid sparing effect of pregabalin in the perioperative period.

Study type: Interventional.

Study design: Randomized, double-blind, placebo-controlled, parallel assignment, efficacy study.

Hypothesis

The preoperative administration of pregabalin 150 mg orally as premedication will suppress the stress response to intubation without causing hemodynamic compromise and reduce perioperative fentanyl consumption in patients undergoing OPCAB grafting.

Objectives of the study

The objective of this study was to assess the possible effects of pregabalins on attenuation of the hemodynamic response to oropharyngeal instrumentation and the opioid sparing.

MATERIALS AND METHODS

The study was approved by the hospital ethical committee. After obtaining informed and written consent, 60 adult patients scheduled for elective OPCAB surgery under general anesthesia in Sri Ramachandra Medical College and Research Institute between July and December 2010 were enrolled in a double-blind, randomized study. The patients were randomly assigned to two groups of 30 each, using a computer-generated randomized list. The control group received a placebo capsule similar to pregabalin and the pregabalin group received pregabalin 150 mg (Lyrica capsules, manufactured by Pfizer Co., India). Both groups received their tablets orally, 60 min before surgery.

Exclusion criteria

1. Ejection fraction of less than 50%.
2. Preoperative left bundle branch block.
3. Known sensitivity to pregabalin.
4. Documented pre-existing chronic pain on or off analgesics.
5. Seizure disorders.
6. Patients who were taking pregabalin or gabapentin.
7. Patients on chronic neuroleptic medications and taking tricyclic antidepressants or serotonin and norepinephrine re-uptake inhibitors.
8. Age more than 70 years.
9. Pregnant or breast-feeding females.
10. Anticipated difficult airway.
11. Severe systemic disorders (e.g., insulin-dependent diabetes mellitus, uncontrolled hypertension, kidney or liver insufficiency, and severe respiratory disorder).

Study design

The day before surgery, all patients were visited for pre-anesthesia assessment and to explain the study protocol. All the patients received oral diazepam 10 mg and pantoprazole 40 mg the evening before surgery and morning of surgery. The patients were randomly divided into two equal groups using a computer-generated table of random numbers, to receive the medication orally 60 min before surgery. Those enrolled in the pregabalin group received 150 mg of pregabalin, whereas those in the control

group received placebo (capsule similar to pregabalin). The study drug was prepared by the pharmacy and an appropriate code number was assigned. Angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists were stopped at least a day prior to surgery. Calcium channel blockers were stopped on the day of surgery, while beta-blockers were continued. Medication administration and data collection were performed in a double-blind manner, so that neither the patients nor the healthcare personnel were aware of the medication assignment. The coding remained blinded until the end of the study.

On arrival in the operating room, noninvasive monitors (electrocardiography – II and V leads, noninvasive blood pressure, pulse oximetry, and bispectral index monitor) were commenced. A 16-G intravenous cannula was inserted in an appropriate anterior cubital vein and a 20-G radial artery cannula was inserted for direct arterial blood pressure measurements and to obtain blood samples. A 7-F pulmonary catheter was introduced via a 9-F introducer sheath into the right jugular vein and it was advanced to a wedge position under continuous pressure monitoring. Monitoring included direct arterial blood pressure, pulmonary arterial pressures, nasopharyngeal temperature, urine output, and capnography. All the cannulations were performed under local anesthesia.

After 3 min of preoxygenation, general anesthesia was induced with intravenous administration of fentanyl 5 mcg/kg, midazolam 50 mcg/kg, and 4 mg/kg thiopentone. To facilitate laryngoscopy and intubation, vecuronium bromide 0.1 mg/kg was administered intravenously. Later, laryngoscopy using Macintosh blade size 3 or 4 and intubation using endotracheal tubes (size 7.0–8.5) were performed by an experienced anesthesiologist. After tracheal intubation, the lungs were mechanically ventilated to maintain endtidal carbon dioxide (CO_2) tension between 30 and 35 mmHg. Anesthesia was maintained with a 50% nitrous oxide in oxygen and sevoflurane to titrate bispectral index score 40–60. An intermittent vecuronium bromide 1 mg was administered when required. After completion of the surgery all the patients were transferred to the intensive care unit for postoperative management. Intravenous fluids were administered to maintain the diastolic pulmonary artery pressure of 14 mmHg. Ephedrine (3 mg) was administered if hypotension occurred. (Hypotension was defined as a decrease in the systolic arterial pressure <90 mmHg or a decrease of >30% from baseline values for >60 sec.).

Postoperative care

Intravenous infusion of propofol was commenced in the intensive care unit at a rate of 1 mg/kg/h until the patients reached extubation criteria. They were extubated once they met the following criteria:

1. Awake and cooperative.
2. Core temperature greater than 36.5°C.
3. Blood draining through the chest drainage tube less than 100 mL/h.
4. Urine output >0.5 mL/kg/h.
5. Partial pressure of arterial oxygen ≥70 mmHg at an inspired oxygen fraction <0.5.
6. Partial pressure of arterial CO_2<50 mmHg and a spontaneous respiratory rate 20 or less at a pressure support ventilation of 10 cm H_2O.
7. No life-threatening arrhythmias.
8. Stable hemodynamics.
9. No evidence of new myocardial ischemia.

No attempt was made to pharmacologically reverse any residual neuromuscular blockade. Time to extubation was recorded in each patient. Postoperatively fentanyl 0.5 mcg/kg was given whenever visual analog scale (VAS) was 4 or more (0 representing no pain and 10 the worst imaginable pain). From the first postoperative day onward all of the patients received the following medications routinely: Enoxaparin 40 mg/day subcutaneously, clopidogrel 75 mg/day, aspirin 75 mg/day, to inhibit platelet aggregation, and 20 mg/day pantoprazole for gastric protection.

The primary outcome measures were hemodynamic response to intubation and fentanyl consumption during surgery and 0–24 h after operation. Secondary outcome measures were postoperative pain score and sedation score and side-effects of nausea and vomiting and dizziness.

Assessment of outcomes

Preoperative variables were noted to describe the population under study, co-morbidities such as diabetes mellitus, hypertension, and history of myocardial infarction were noted. Other variables such as ejection fraction, presence of regional wall motion abnormalities, number of vessels diseased, and preoperative medication (beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, and diuretics) were also recorded.

Outcome measures for the study were assessed by a research or acute pain service nurse who was blinded

to patient group assignments. The patients were asked to quantify their pain on a VAS between 0 and 10.

Sedation scores was measured on a numerical score of 1–6 (Ramsay sedation scale, 1: Patient is anxious and agitated or restless, or both, 2: Patient is co-operative, oriented, and tranquil, 3: Patient responds to commands only, 4: Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5: Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6: Patient exhibits no response).

Systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and pulmonary capillary wedge pressure were recorded after arrival to operation theatre (baseline), 3 min after administration of induction, and 1, 3, and 5 min after the intubation.

The sedation scores were recorded after arrival at the operation theatre (baseline) and 6, 12, and 24 h after shifting to the intensive care unit. VAS scores were recorded 6, 12, and 24 h after shifting to the intensive care unit.

The dose of fentanyl requirements during surgery and 24 h postoperatively were recorded. The duration of ventilation and intensive care unit stay, respiratory depression (respiratory rate <8 breaths/min), and nausea and vomiting, drowsiness, and headache was also recorded.

Statistics

Pre hoc power calculation suggested that a minimum of 25 patients per group would detect a 15% difference in hemodynamic response to laryngoscopy and endotracheal intubation and perioperative fentanyl requirement between groups after intubation (α=0.05, β=0.2). To take care of any dropouts, we enrolled 30 patients in each group. All data were presented as mean±standard deviation. All data were analyzed by Student's *t* test (independent samples *t* test) and Chi-square test and Fisher's exact test wherever applicable. Nonparametric tests (Wilcoxon signed rank tests (2 tailed)) were used whenever the mean value was less than two times the standard deviation. A *P* value <0.05 was considered statistically significant. The package SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULTS

The demographic data were comparable between the two groups as shown in Table 1. The distributions of risk factors, such as hypertension, diabetes mellitus, and history of myocardial infarction in the two groups were statistically insignificant [Table 1]. The distribution of antihypertensive drugs (beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics) between the two groups are shown in Table 2. The number of patients with regional wall motion abnormality, the mean ejection fraction, and the number of diseased coronary vessels between the two groups was insignificant [Table 2].

The baseline hemodynamic parameters between the two groups were similar (no significance, $P>0.05$) and clinically no difference was observed. The increase in heart rate 1 min after intubation was significantly higher in the control group in comparison with the pregabalin group. The heart rate changes at other time periods between two groups were insignificant. The mean systolic arterial pressure measured during different time periods between the two groups was significantly lower in the pregabalin group except the baseline systolic arterial pressure. The mean diastolic arterial pressure measured during different time periods between the two groups was significantly lower in pregabalin group except the baseline diastolic arterial pressure [Table 3].

Table 1: Patient characteristics and preoperative variables

Variable	Control group	Pregabalin group	*P* value
Age (years)	57.2 ± 7.6	60.1 ± 8.6	0.175
Weight (kg)	66.00 ± 9.4	66.44 ± 8.08	0.847
Height (cm)	164.18 ± 8	164.63 ± 7.10	0.819
Sex (M:F)	20:10	22:8	0.573
Hypertension	21 (70)	21 (70)	1.000
Diabetes mellitus	18 (60)	21 (70)	0.417
Myocardial infarction	11 (36.7)	12 (40)	0.791

M:F- Male:Female, Values are given as mean ± standard deviation, or number of patients(%).

Table 2: Preoperative variables

Variable	Control group	Pregabalin group	*P* value
Beta-blockers	26 (86.7)	24 (80)	0.488
Calcium channel blockers	3 (10)	5 (16.7)	0.448
ACEI and ARB	13 (43.3)	12 (40)	0.793
Diuretics	0	2 (6.7)	0.150
RWMA	11 (36.7)	12 (40)	0.791
Ejection fraction	59.93 ± 7.79	61.23 ± 6.03	0.473
No. of diseased vessels	2.57 ± 0.50	2.60 ± 0.56	0.810

ACEI - Angiotensin-converting enzyme inhibitors; ARB - Angiotensin receptor blockers; RWMA - Regional wall motion abnormality, Values are given as mean ± standard deviation, or number of patients(%).

Table 3: Hemodynamic data

Variable	Group	B	AI	1st	3rd	5th
HR	Control	74.13 ± 10.79	71.87 ± 9.65	85.30 ± 13.34	80.87 ± 11.24	75.50 ± 9.31
	Pregabalin	73.33 ± 11.58	71.2 ± 9.89	78.77 ± 10.72	77.67 ± 11.25	73.47 ± 10.54
	P value	0.783	0.793	0.041*	0.275	0.432
	Pregabalin	73.33 ± 11.58	71.2 ± 9.89	78.77 ± 10.72	77.67 ± 11.25	73.47 ± 10.54
SBP	Control	150.1 ± 21.21	105.63 ± 15.22	152.37 ± 24.61	136.23 ± 23.13	123.8 ± 22.38
	Pregabalin	148.83 ± 23.28	97.43 ± 15.31	122.07 ± 23.41	110.5 ± 18.46	104.73 ± 14.73
	P value	0.826	0.042*	0.000*	0.000*	0.000*
DBP	Control	74.37 ± 8.78	60.7 ± 9.48	88.07 ± 13.32	78.27 ± 12.50	72.2 ± 11.33
	Pregabalin	77.1 ± 10.79	55.13 ± 9.29	70.17 ± 13.48	65.47 ± 11.67	64.9 ± 11.05
	P value	0.286	0.025*	0.000*	0.000*	0.014*
MAP	Control	103.43 ± 12.37	77.43 ± 11.59	112.8 ± 18.61	100.47 ± 16.54	91.67 ± 16.14
	Pregabalin	104.8 ± 13.52	70.3 ± 11.68	89.73 ± 179	82.03 ± 14.51	77.87 ± 14.12
	P value	0.685	0.021*	0.000*	0.000*	0.001*
PCWP	Control	9.53 ± 3.01	8.67 ± 2.35	10.67 ± 3.68	9.37 ± 2.91	9.4 ± 2.28
	Pregabalin	8.1 ± 2.88	7.53 ± 2.83	7.9 ± 3.06	7.4 ± 2.71	7.57 ± 2.59
	P value	0.065	0.098	0.002*	0.009*	0.005*

*Statistically significant *P* values. HR - Heart rate; SBP - Systolic blood pressure; DBP - Diastolic blood pressure; MAP - Mean arterial pressure; PCWP - Pulmonary capillary wedge pressure; B - Baseline; AI - 3 min after induction; 1st - First minute; 3rd - Third minute, 5th - Fifth minute after intubation. Values are expressed as mean±standard deviation

A significant change of the mean arterial pressure was noticed between the two groups. It was higher in the control group except the baseline mean arterial pressure, which was similar in both the groups [Table 3]. The mean pulmonary capillary wedge pressure measured at 1, 3, and 5 min after intubation showed significantly higher values in the control group compared with the pregabalin group. The baseline and post-induction measurements were similar in both the groups [Table 3]. The mean duration of intubation (s) between groups showed no statistical significance [Table 4]. The mean duration of surgery, ventilation, intensive care unit stay, and the number of vessels grafted were similar in both the groups [Table 4].

There were no significant differences in the consumption of fentanyl between the two groups during surgery and 0–24 h after surgery in the intensive care unit [Table 5]. There were also no significant differences in the VAS between the groups at any time point. There was no significant difference between the groups in the VAS measured at 6, 12, and 24 h after surgery. Ramsay sedation scores measured after arrival to operation theatre (baseline), 6, 12, and 24 h after surgery were also similar between the groups [Table 6]. Although the incidence of nausea was high in the control group, the difference was statistically not significant. No patient in our study group developed vomiting or dizziness during the study period.

Table 4: Perioperative variables

Variable	Control group (mean±SD)	Pregabalin group (mean±SD)	*P* value
Duration of intubation (seconds)	9.27 ± 2.22	8.93 ± 1.98	0.543
Duration of surgery (min)	246.33 ± 47.41	261.83 ± 58.21	0.263
Duration of ventilation (min)	622 ± 308.07	636.33 ± 280.73	0.851
Number of vessels grafted	2.53 ± 0.68	2.57 ± 0.72	0.855
Duration of intensive care unit stay (days)	2.8 ± 0.92	3.27 ± 1.08	0.078

SD - Standard deviation

Table 5: Fentanyl required during study

Fentanyl (mcg)	Control group (mean±SD)	Pregabalin group (mean±SD)	*P* value
Intraoperative	1143.33 ± 310.65	1070.0 ± 362.60	0.636
24 h Postoperative	251.67 ± 181.47	241.67 ± 178.87	0.638
Total fentanyl (intraop and 24 h postoperative)	1395.00 ± 375.7	1311.67 ± 392.19	0.785

SD - Standard deviation

Table 6: Visual analog and Ramsay sedation scores

	Variable (h)	Control group (mean±SD)	Pregabalin group (mean±SD)	*P* value
Visual analog score	6	2.20 ± 0.61	2.03 ± 0.61	0.296
	12	2.13 ± 0.57	2.03 ± 0.71	0.553
	24	2.00 ± 0.64	2.07 ± 0.74	0.711
Ramsay sedation score	Preop	2.07 ± 0.27	2.17 ± 0.37	0.235
	6	2.47 ± 0.50	2.63 ± 0.49	0.201
	12	2.33 ± 0.47	2.47 ± 0.50	0.300
	24	2.23 ± 0.43	2.33 ± 0.47	0.399

SD - Standard deviation

DISCUSSION

This study demonstrated that a single oral dose of 150 mg pregabalin administered 1 h before surgery attenuated

the pressor response to tracheal intubation in adults but the drug did not show any effect on intraoperative and postoperative opioid consumption or postoperative pain relief. The elevation of the pulse rate and blood pressure may be transient, variable, and unpredictable. Usually these changes are well tolerated by healthy individuals. However, such changes may be deleterious in patients with severe hypertension, coronary artery disease, or intracranial hypertension. A variety of drugs have been used to control this hemodynamic response; they are vasodilators, beta-blockers, calcium channel blockers, alpha-2 agonists, and opioids.[20-22]

Although many studies proved the efficacy of gabapentin to attenuate intubation response, only one study showed the efficacy of pregabalin to suppress intubation response.[19] The author's result correlates well with the report of Eren *et al*.[19] They determined the effect of a single dose of pregabalin 150 mg, administered 1 h prior to surgery on reducing the cardiovascular response and stated that 150 mg of pregabalin had significantly decreased the mean arterial pressure and heart rate response to tracheal intubation of the patients undergoing lumbar discal hernia repair under general anesthesia. The mechanism by which pregabalin attenuates the hemodynamic response to laryngoscopy and intubation remains unknown.

Pregabalin inhibits membrane voltage-dependent Ca^{2+} channels; it is possible that it may act in a manner similar to calcium channel blockers in controlling the hemodynamic response. Memis and co-workers reported that the inhibitions of Ca^{2+} efflux from muscle cells with a consequent inhibition of smooth muscle relaxation might explain the effectiveness of gabapentinoids in the relaxation of laryngoscopy.[17]

Ali *et al*., demonstrated that administration of gabapentinoids did not affect basal plasma catecholamine (epinephrine and norepinephrine) concentrations before intubation, failed to attenuate the catecholamine response to intubation and conversely, enhanced the increase of plasma norepinephrine concentration.[18] The results of this study also showed that despite higher plasma concentration of norepinephrine in patients receiving gabapentin than in the control group after intubation, the increase in mean arterial pressure and heart rate was lower in the gabapentin group during the study period. The cardiovascular response to catecholamines may be attenuated by gabapentinoids without affecting their secretion. The important determinant of the level of arterial pressure to tracheal intubation may be reactivity to norepinephrine and not the plasma concentration.[23] One of the drawbacks of our study was that the plasma concentration of stress mediators was not measured.

In this study systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, pulmonary capillary wedge pressure, and heart rate baseline values did not differ significantly between the controls and the patients pretreated with pregabalin. The analgesic and opioid-sparing effect of pregabalin given as premedication appears to be limited. The use of pregabalin in acute postoperative pain management has been evaluated in recent studies. These studies sought to determine whether perioperative pregabalin was effective in reducing postoperative pain and whether it had opioid-sparing effects. However, differences in the pregabalin dosages and types of surgery have yielded contrasting results. A study investigating pain relief after dental extraction showed that 400 mg pregabalin administered after operation was more effective than ibuprofen in attenuating acute post-procedural pain.[24]

Reuben and colleagues observed that in patients undergoing lumbar laminectomy, pregabalin 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 the most effective.[25] In another clinical trial, Jokela and colleagues observed that perioperative administration of pregabalin 300 mg before and after laparoscopic hysterectomy decreases oxycodone consumption, but is associated with an increased incidence of adverse effects.[26] Based on the existing data, a more pronounced analgesic and opioid-sparing effect of pregabalin was anticipated but not seen in the present study.

In contrast to these trials, the authors did not find any analgesic effect. The possible explanations are as follows. The dose of pregabalin administered may have been sub-therapeutic. Hill *et al*.,[24] found no difference between pregabalin 50 mg and placebo, but a statistically significant reduction in pain and pain intensity at a dose of 300 mg. Reuben *et al*., evaluated the comparative analgesic efficacy of pregabalin 150 mg and celecoxib 200 mg when administered both before and after spinal fusion surgery. Analogous to celecoxib, pregabalin reduced postoperative opioid usage compared with a placebo. However, neither drug was found to reduce opioid-related side-effects in the postoperative period.[25] We chose to study a dose

of 150 mg because the recommended starting dose is 150 mg/day and because dizziness and somnolence, the most common side-effects, generally begin shortly after initiation of dosing. We particularly wished to avoid these side-effects. It appears that administration of a larger dose, which might further increase the incidence or severity of side-effects, would not be appropriate in this particular surgical population. This could be tested in future research.

Besides being analgesic, pregabalin has anxiolytic properties. In fact, in the present study the level of sedation was similar after premedication with placebo or pregabalin 150 mg. The missing effect on anxiety may be caused by the administration of the drug on one single day. Dizziness and somnolence are the most common side-effects of long-term pregabalin use during the treatment of chronic pain. However, somnolence and dizziness with pregabalin were not reported in a majority of the postoperative pain studies in which pregabalin was only used preoperatively. Similarly, in the present study, sedation scores were similar in both the groups. No patient in this study developed pruritus.

The present study showed that patients in the pregabalin group experienced less nausea than the patients in the placebo group, although it is statistically not significant. The low incidence of postoperative nausea after the 150 mg dose of pregabalin may be related to the opioid-sparing effect. In a previous study with pregabalin, vomiting was one of the most frequently reported side-effects,[24] whereas in another the incidence of nausea was lower after the perioperative administration of celecoxib and pregabalin.[25] The mechanism of pregabalin in the prevention of postoperative nausea and vomiting is unknown but it could possibly be due to the indirect effect of opioid-sparing or a direct effect on tachykinin activity. A similar drug, gabapentin, has been shown to be useful in reducing chemotherapy-induced nausea in an open-label preliminary study.[27] Mitigation of tachykinin neurotransmitter activity by gabapentin has been a postulated mechanism. To demonstrate the difference in the incidences of postoperative nausea and vomiting, a substantially larger sample size is required.

Limitations

1. Stress mediators such as endogenous plasma catecholamines or cortisone were not measured.
2. Evaluation of the dose response or the effect of continuation of therapy was not done.
3. Fentanyl was not continuously infused during surgery and postoperatively.
4. Dynamic component of mechanical hyperalgesia (pain during mobilization) was not assessed.

CONCLUSION

Pregabalin administered as a single oral dose an hour prior to OPCAB produces the following effects:

1. Suppresses reflex tachycardia and hypertension related to laryngoscopy and intubation of trachea in patients coming for elective OPCAB grafting.
2. The analgesic and opioid-sparing effect of pregabalin given as premedication was not apparent.
3. Does not produce dizziness and visual disturbance (including blurred vision and diplopia).

REFERENCES

1. Kissin I. Preemptive analgesia. Anesthesiology 2000;93:1138-43.
2. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci Lett 1986;64:221-5.
3. Frampton JE, Scott LJ. Pregabalin: In the treatment of painful diabetic peripheral neuropathy. Drugs 2004;64:2813-20; discussion 2821.
4. Woolf C, Chong MS. Preemptive analgesia–treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362-79.
5. Wilder-Smith OH. Pre-emptive analgesia and surgical pain. Prog Brain Res 2000;129:505-24.
6. Wilder-Smith OH. [Pre-emptive analgesia]. Anaesthesist 1995;44 Suppl 3: S529-34.
7. Fink K, Dooley DJ, Meder WP, Suman-Chauhan N, Duffy S, Clusmann H, *et al*. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology 2002;42:229-36.
8. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004;45 Suppl 6:13-8.
9. Frampton JE, Foster RH. Pregabalin: In the treatment of postherpetic neuralgia. Drugs 2005;65:111-8; discussion 119-20.
10. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain–a systematic review of randomized controlled trials. Pain 2006;126:91-101.
11. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005;100:1394-9.
12. Pandey C, Priye S, Ambesh S, Singh S, Singh U, Singh P. Prophylactic gabapentin for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: A randomized, double-blind, placebo-controlled study. J Postgrad Med 2006;52:97-100.
13. Shneker BF, McAuley JW. Pregabalin: A new neuromodulator with broad therapeutic indications. Ann Pharmacother 2005;39:2029-37.
14. Kavoussi R. Pregabalin: From molecule to medicine. Eur Neuropsychopharmacol 2006;16 Suppl 2:128-133.
15. Kaya FN, Yavascaoglu B, Baykara M, Altun GT, Gülhan N, Ata F. Effect of oral gabapentin on the intraocular pressure and haemodynamic responses induced by tracheal intubation. Acta Anaesthesiol Scand 2008;52:1076-80.
16. Fassoulaki A, Melemeni A, Paraskeva A, Petropoulos GGabapentin attenuates the pressor response to direct laryngoscopy and tracheal intubation. Br J Anaesth 2006;96:769-73.
17. Memis D, Turan A, Karamanlioglu B, Seker S, Ture M. Gabapentin reduces cardiovascular responses to laryngoscopy and tracheal intubation. Eur J Anaesthesiol 2006;23:686-90.

18. Ali AR, El Gohary M, H. Salah El-din A, El-Kerdawy HM, Essa HH. Efficacy of Preoperative Oral Gabapentin in Attenuation of Neuro-Endocrine Response to Laryngoscopy and Endotracheal Intubation. J Med Sci 2009;9:24-9 .
19. Eren G, Kozanhan B, Hergunsel O. Pregabalin Blunts Cardiovascular Responses To Laryngoscopy And Tracheal Intubation. J Anesthesiol Reanim 2009;7:82-7.
20. Kovac Al. Controlling the hemodynamic response to laryngoscopy and endotracheal intubation. J Clin Anesth 1996;8:63-79.
21. Maguire AM, Kumar N, Parker Jl, Rowbotham DJ, Thompson JP. Comparison of effects of remifentanil and alfentanil on cardiovascular response to tracheal intubation in hypertensive patients. Br J Anaesth 2001;86:90-3.
22. Habib AS, Parker JL, Maguire AM, Rowbotham DJ, Thompson JP. Effects of remifentanil and alfentanil on the cardiovascular responses to induction of anaesthesia and tracheal intubation in the elderly. Br J Anaesth 2002;88:430-3.
23. Pillipp T, Distller A, Cordes D. Sympathetic nervous system and blood-pressure control in essential hypertension. Lancet 1978;2:959-63.
24. Hill CM, Balkenohl M, Thomas DW, Walker R, Mathé H, Murray G. Pregabalin in patients with postoperative dental pain. Eur J Pain 2001;5:119-24.
25. Reuben SS, Buvanendran A, Kroin JS, Raghunathan K. The analgesic efficacy of celecoxib, pregabalin, and their combination for spinal fusion surgery. Anesth Analg 2006;103:1271-7.
26. Jokela R, Ahonen J, Tallgren M, Haanpaa M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain 2008;134:106-12.
27. Guttuso T Jr, Roscoe J, Griggs J. Effect of gabapentin on nausea induced by chemotherapy in patients with breast cancer. Lancet 2003;17:1703-5.

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