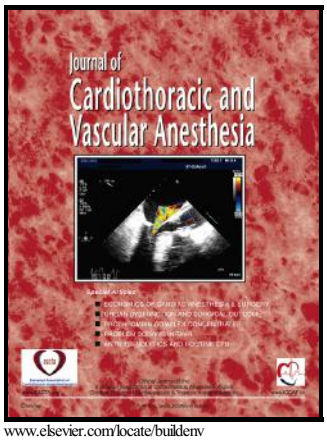

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Effect of Perioperative Pregabalin on Post operative Quality of Recovery in Patients Undergoing Off Pump Coronary Artery Bypass Grafting (OPCABG) - Prospective, Randomized, Double Blind Trial

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Abstract:

Objectives:

Use of pregabalin is increasing in cardiac surgical patients. But studies are lacking on its impact on postoperative recovery using comprehensive scoring systems. The authors tested the hypothesis that perioperative oral pregabalin improves the postoperative quality of recovery as assessed by QoR-40 questionnaire in patients undergoing OPCABG.

Design:

This was a randomized, double blind, placebo-controlled study.

Settings:

Tertiary care level hospital.

Participants:

Patients undergoing OPCABG.

Interventions:

The patients were randomized in two groups as pregabalin group (those receiving Cap. Pregabalin 150 mg per orally one hour before surgery & continued for two days (75 mg twice a day) starting after extubation; N=37) and control group (those receiving two similar looking multivitamin capsule at similar timings; N=34). The QoR-40 scores were noted preoperatively and 24 hours post extubation.

Measurements and Main Results:

Both groups were comparable in terms of preoperative patient characteristics and baseline QoR-40 scores. Global scores were significantly improved in the pregabalin group compared with the control group in postoperative period (177± 9 *v* 170± 9; p =0.002). QoR-40 values in the dimensions of emotional state (p = 0.005), physical comfort (p = 0.04), and pain (p =0.02) were improved in pregabalin group.

Conclusions:

Perioperative Pregabalin improves post-operative quality of recovery as assessed by QoR-40 questionnaire in patients undergoing Off Pump CABG. Perioperative pregabalin offers advantages beyond better pain control like improved physical comfort and better emotional state; hence its use in perioperative period is recommended.

Introduction:

As the safety of anesthesia and surgery has improved, the assessment of the quality of postoperative recovery has become an increasingly important outcome measure. An important component of recovery from anesthesia and surgery is patient perception of quality of health in the early postoperative period. The Quality of Recovery-40 (QoR-40) is a 40-item scoring system specifically developed to measure health status after anesthesia [1]. A systematic review of instruments used to measure patient based recovery outcomes determined that the QoR-40 was the only assessment tool that fulfilled all eight eligibility criterions [2]. Another meta analysis enrolling 3459

patients from 17 studies concluded that QoR- 40 is well suited to measure quality of postoperative recovery [3].

Pregabalin is newer "gabapentionoid" which reduces excitability of dorsal horn neurons after tissue damage. Pregabalin has been proven to improve various aspects of recovery after surgery. Pregabalin is associated with a significant reduction in pain scores at rest and during movement and opioid consumption at 24 h of surgery compared with placebo and also patients receiving pregabalin have less postoperative nausea and vomiting and pruritus compared with placebo [4]. Use of pregabalin is increasing in cardiac surgical patients. Most of the previous studies have focused on improvement in pain scores after cardiac surgery [5-7]. But none of these studies have used a comprehensive scoring system to assess impact on postoperative recovery.

The authors tested the hypothesis that perioperative oral pregabalin improves the postoperative quality of recovery as assessed by QoR-40 questionnaire in patients undergoing OPCABG.

Methods:

This was a prospective, randomized, double blind, placebo-controlled study conducted at a tertiary care level hospital. The institutional review board approved the study, and written informed consent was obtained from all subjects. Eighty adult patients of either sex scheduled for elective OPCABG were enrolled in this study. The exclusion criteria were: Hypersensitivity to pregabalin, preoperative use of pregabalin; emergency surgery or emergency conversion to on pump CABG; ejection fraction (EF) <30%; preoperative major organ dysfunction (Sr. creatinine more than 2 mg/dL, deranged liver function tests, preoperative neurologic deficit); preoperative use of inotropic agents or an intra-aortic balloon pump, prolonged ventilator support in postoperative period or unwillingness of the patient.

The patients were randomized in two groups as pregabalin group (those receiving Cap. Pregabalin 150 mg per orally one hour before surgery & continued for two days (75 mg twice a day) starting after extubation) and control group (those receiving two similar looking multivitamin capsule as placebo per orally one hour before surgery & continued for two days (one capsule 12 hourly) starting after extubation).

After the patients were found suitable for inclusion in the study, they were explained about nature of study in their vernacular language and informed consent was obtained for participation in the study from all patients. The baseline QoR-40 questionnaire was provided to subjects and was noted by investigator who is blinded for the study drug. An anesthetist blinded to group assignment administered the drug as per computer generated randomization chart (either pregabalin or placebo multivitamin) orally with sips of water to the patient approximately one hour prior to surgery. In the preoperative area patient were monitored for vital parameters before shifting to operation theatre.

Standard perioperative monitoring consisted of 5-lead electrocardiography, pulse oximetry, capnography, femoral artery catheterization, pulmonary artery catheterization, and trans-esophageal echocardiography. Anesthesia was induced with propofol, 1 to 2 mg/kg, and midazolam, 2 to 3 mg. Fentanyl was administered as bolus doses 2 μg/kg during induction and 1-2 μg/kg boluses given at an interval of an hour as per standard institute protocol. Total dose of intraoperative fentanyl used was noted. Neuromuscular blockade was achieved with vecuronium, with additional boluses given as necessary. The patients were ventilated with a tidal volume of 6 to 8 mL/kg, and the respiratory rate was adjusted to keep end-tidal carbon dioxide between

30 and 34 mmHg using a 50% oxygen and air gas mixture. Anesthesia was maintained with isoflurane (0.5 -3 volume%). Surgery was performed via a median sternotomy approach. Internal thoracic arteries and saphenous veins were used as conduits in CABG patients. An initial dose of 200 U/kg of heparin was administered to achieve anticoagulation (activated coagulation times greater than 300 seconds). Normothermia was attempted all throughout the surgery with external heating mattresses. Protamine sulfate (1 mg per 100 units of heparin) was used to reverse anticoagulation.

Postoperatively each patient was shifted to postoperative ICU where monitoring was done by an anesthetist blinded for the drug. After patient fulfilled criterions for extubation (responsive, negative inspiratory force >_20 mm Hg, core temperature >36.50C, arterial pH >7.3, chest tube drainage <100 ml/h and absence of uncontrolled dysrhythmia), neuromuscular blockade was reversed and attending anesthetist extubated the patient. Time required for extubation was noted. Postoperative analgesia regimen consisted of Inj. tramadol (2mg/kg given twice a day) and Inj. Paracetamol (1 gm. infusion given four times a day). Rescue analgesia in the form of fentanyl bolus 1 µg/kg was given when VAS score was more than 4.

Intraoperative and ICU data recorded on data-collection forms by the anesthesia care team and the ICU nursing staff respectively were collected. That included patients' demographic data, height, weight, co-morbidities, preoperative drug usage, number of coronary vessels involved, and number of grafts, perioperative blood transfusions, inotropic support, perioperative opioid, benzodiazepine use and post-operative major complications.

The QoR-40 form was again provided to patients for completion postoperatively. An intensivist blinded for the study drug recorded verbal responses by patients. The QoR-40 was completed at approximately 24 hours post extubation.

The primary outcome variable of this investigation was the postoperative QoR-40 score. A previous study by Myles et al in cardiac surgical patients reported postoperative day (POD) 1 global QoR-40 scores of 163 points [8]. Assuming a QoR-40 score of 163 in the control group, 2 groups with sample sizes of 34 subjects each can achieve 80% power to detect an improvement of 10 points in the pregabalin group (173) with estimated group standard deviations of 12 and with a significance level (alpha) of 0.01 using a 2-sided 2-sample t test.

Discrete data was compared using the Fisher exact test. Ordinal data and continuous

data that were not normally distributed were presented as the median and range. These data were compared among groups using the Mann-Whitney U test. The median differences and their 99% confidence intervals were calculated. Normally distributed continuous data was presented as the mean and standard deviation. These data was compared using the unpaired t test. A p value <0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS) version 16.0.0 for Windows (SPSS Inc., Chicago) was used for analysis.

Results:

During study period 85 patients were considered eligible, but five patients were not willing to participate or could not complete baseline QoR-40 questionnaire. A total of 80 patients were enrolled in this investigation; nine were excluded from the study for various reasons (one patient was converted to emergency on pump due to hemodynamic instability; four patients required prolonged ventilation or noninvasive mask ventilation which prevented them from satisfactory response; two patient developed paralytic ileus postoperatively preventing oral medication; one patient developed post op delirium; one patient refused to continue in the study). Final analysis included 71 patients who received the study drug (37 in the pregabalin group and 34 in the control group).

Both groups were comparable in terms of preoperative patient characteristics as presented in Table 1.

Intraoperative variables also were similar between groups, with no differences observed in the duration of anesthesia, anesthesia medications, the administration of crystalloids and blood products, the use of vasoactive medication. The postoperative ventilation time also was similar in both groups as demonstrated in Table 2.

Hemodynamic variables recorded in the operating room and ICU did not differ between the pregabalin and control groups at any time as demonstrated in Table 3. Baseline QoR-40 scores measured preoperatively did not differ between the pregabalin and control groups. Global scores (median [range]) were significantly improved in the pregabalin group compared with the control group in postoperative period (177± 9 *v* 170± 9; p =0.002). QoR-40 values in the dimensions of emotional state (p = 0.005), physical comfort (p = 0.04), and pain (p =0.02) were improved in pregabalin group. No differences between groups were observed in the dimensions of physical independence and psychological support (Table 4). The number of patients requiring rescue analgesia was significantly higher in placebo group (4 vs. 13; p< 0.001). Side effects in terms of dizziness were noted more frequently in pregabalin group (1vs. 5; p =0.01).

Discussion:

The main finding of the study is that perioperative oral pregabalin improves the postoperative quality of recovery as assessed by QoR-40 questionnaire in patients undergoing OPCABG.

The mortality rates after OPCABG have decreased dramatically with increasing experience of teams. Now the interventions that reduce the morbidity and improve patient satisfaction are gaining importance. An important component of recovery from anesthesia and surgery is patient perception of quality of health in the early postoperative period. The QoR-40 is a 40-item scoring system specifically developed to measure health status after anesthesia [1]. Recently, a systematic review of seven instruments used to measure patient based recovery outcomes was conducted. It demonstrated that the QoR-40 was the only assessment tool that fulfilled all the eight criteria; viz appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability, and feasibility [2]. In another quantitative systematic review of studies evaluating psychometric properties of the QoR-40 evaluated 17 studies enrolling sample of 3459 patients from nine countries. The authors confirmed content, construct, and convergent validity and reliability. The clinical utility of the QoR-40 instrument was supported by high patient recruitment into evaluation studies (97%), and an excellent completion and return rate (97%). The mean time to complete the QoR-40 was 5.1 (95% CI: 4.4–5.7) min [3].

The QoR-40 has been used previously to assess the impact of anesthetic interventions on recovery after cardiac surgery [9, 10]. There is also a relationship between quality of recovery in the days and weeks after surgery, with quality of life up to 3 months after cardiac surgery [8]. Hence we used this valid scoring system to assess impact of perioperative oral pregabalin in patients undergoing OPCABG.

Gabapentinoids (gabapentin and pregabalin) are relatively new drugs, which were originally introduced as anti-epileptics and also have analgesic, anticonvulsant, and anxiolytic effects. Pregabalin is absorbed throughout the small intestines and demonstrates linear uptake without transporter saturation at therapeutic concentrations hence it has higher efficacy than gabapentin. Pharmacokinetic interactions are minimal. Time taken for peak plasma levels to achieve with pregabalin is only one hour compared to two hors that of gabapentin [11]. Mean elimination half-life of

pregabalin is 6.3 hours and steady state is achieved within 24–48 hours. Therefore, pregabalin could be a better choice for postoperative analgesia.

In a recent systematic review and meta-analysis of 55 studies on pregabalin (N= 4155 patients; 2270 received pregabalin and 1885 served as control) the authors found that the perioperative administration of pregabalin was associated with a statistically significant reduction in pain scores at rest (mean difference of 0.81 at 2 h and 0.38 at 24 h), pain scores during movement (mean difference of 0.58 at 2 h, and 0.47 at 24 h), and opioid consumption (mean difference of 2.09mg morphine equivalents at2h, and 8.27mg at 24h)after surgery compared with placebo. This meta-analysis included only three studies in cardiac surgical patients [4].

Use of Gabapentinoids is increasing in cardiac surgical patients. Ucak [12] et al and Menda et al [13] demonstrated that perioperative oral gabapentin significantly reduced postoperative opioid consumption and postoperative pain both at rest and with cough. In elderly patients undergoing cardiac surgery, Pesonen et al [6] used pregabalin 150 mg before cardiac surgery and 75 mg twice a day for 5 days and reported a reduction in opioid consumption by 44% at 24 h and 48% by 5th post-operative day. There was reduced incidence of confusion on the first postoperative day but extubation was delayed when compared with placebo. Three months after operation, patients in the pregabalin group experienced less pain during movement. Similarly Joshi et al [5] in a randomized double blind placebo controlled trial evaluated the efficacy of perioperative pregabalin on acute and chronic post-operative pain after OPCABG surgery. Pain-scores at 6, 12, 24 and 36 h from extubation at rest and at deep breath were less in pregabalin treated patients ($P < 0.05$). Tramadol consumption was reduced by 60% in pregabalin group ($P < 0.001$). Extent of sedation, extubation times and incidence of nausea were comparable. In accordance to literature our study also demonstrated that pain component (comprised of seven aspects of pain) of comprehensive QoR-40 scale was lower ($p= 0.02$) in pregabalin group. It is interesting to note that on similar note, in our study, the proportion of patients requiring rescue analgesia in the form of fentanyl was significantly higher in placebo group ($p< 0.001$).

Baseline QoR-40 scores measured preoperatively did not differ between the pregabalin and control groups (Table 4). Global scores were significantly improved in

the pregabalin group compared with the control group in postoperative period (177± 9 vs. 170± 9; p =0.002). It was observed that in addition to pain component, there was improvement in emotional state (p = 0.005), physical comfort (p = 0.04). The physical comfort dimension quantifies postoperative shivering, restfulness/fatigue, dizziness, nausea, vomiting, and appetite. In meta- analysis mentioned above [4], the incidence of opioid- related side effects (PONV and pruritus) was significantly reduced with pregabalin administration by 38% and 51%, respectively, relative to placebo at 24 h after surgery. Patients receiving pregabalin reported an improved emotional state postoperatively in QoR-40 surveys. The QoR-40 assesses both positive (3 questions; viz. feeling of general well being/ in control/comfortable) and negative (6 questions; viz. feeling anxious/ angry/ depressed/alone, bad dreams or feeling difficulty falling asleep) emotions during recovery from surgery. None of the previous studies in cardiac surgical patients have assessed the effect of pregabalin on postoperative emotional state. Significantly lower preoperative anxiety scores with pregabalin administration were reported in patients undergoing lumbar laminectomy [14,15]. In patients undergoing elective craniotomy for brain tumor excision, the preoperative anxiety level and the quality of sleep were significantly better in the pregabalin group ($p < 0.01$)[16]. So, these findings point towards better emotional state with pregabalin administration.

In a recent study of 204 patients, it was proposed that perioperative interventions that result in a change of 6.3 for the QoR-40 signify a clinically important improvement or deterioration [17]. So, our finding of improvement of QoR- 40 score by seven in postoperative period is clinically important improvement although we had hypothesized improvement of 10 points while calculating size of the study.

Limitations:

There are some limitations to the present study. First, the authors measured QoR-40 score only one time in post operative period, so impact of pregabalin in remaining hospital stay could not be verified. Second, this study included majority of low risk patients, so use of pregabalin cannot be recommended in high-risk patient population. Third, the study was underpowered to detect major side effects of pregabalin like dizziness, visual disturbances.

Conclusions:

Perioperative Pregabalin improves post-operative quality of recovery as assessed by QoR-40 questionnaire in patients undergoing Off Pump CABG. Perioperative pregabalin offers advantages beyond better pain control like improved physical comfort and better emotional state; hence its use in perioperative period is recommended.

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Table 1: Baseline Patient Characteristics

Patient Variables	Pregabalin Group (N=37)	Placebo Group (N=34)
Age (years)	59.27 ± 9.11	60 ± 7.90
Height	160.54 ± 10.33	161.06 ± 8.06
Weight	60.95 ± 11.56	60.06 ± 8.0.6
Female Sex (%)	7 (18.91%)	7 (20.50%)
Hypertension	17 (45.94%)	14 (41.17%)
Diabetes	11 (29.72%)	11 (32.35%)
Smoker/ COPD	9 (24.32%)	8 (23.52%)
Creatinine	1.08 ± 0.27	1.09 ± 0.28
Ejection Fraction	56.35 ± 10.84	55.03 ± 12.08
Diastolic Dysfunction	9 (24.32%)	12 (35.29%)
H/o Recent MI	22 (59.45%)	23 (67%)
Number of diseased Coronaries	2.75	2.77
Left main Stenosis	3	2
Preoperative Medications		
βblockers	32	29
Statins	34	33
ACE Inhibitors	8	8

COPD: Chronic obstructive pulmonary disease; MI: Myocardial Infarction; ACE-Angiotensin Converting Enzyme.

Table2: Peri-operative Variables

Variables	Pregabalin Group (N= 37)	Placebo Group (N=34)	P value
Intraoperative Fentanyl (μg)	422 ± 64	425 ± 74	0.3
Midazolam (mg)	4.68 ± 0.88	4.47 ± 0.78	0.96
Intra Venous Fluids (mL)	1750	1800	0.52
Blood Transfusion	3	2	0.10
Inotropes used (n)	17	15	0.09
Number of Grafts- Median (IQR)	3 (3-4)	3 (3-4)	0.82
Duration of surgery	4.25 ± 0.87	4.24 ± 0.7	0.71
Post operative Ventilation Duration (hours)	5.76 ± 4.3	5.09 ± 3.9	0.92

Table 3: Peri-operative Hemodynamic Parameters

Variable	Pregabalin Group	Placebo Group	P Value
Heart Rate			
Induction	77.51± 15.77	74.47± 11.81	0.36
Incision	79.59± 16.57	75.85± 13.08	0.51
Sternotomy	73.05± 15.80	73.35± 12.09	0.72
Post Grafting	85.70± 14.88	83.88± 11.69	0.57
Post Protamine	85.89±16.57	84.68± 9.93	0.35
ICU Arrival	91.05± 16.90	89.94± 13.96	0.15
Extubation	102.59± 14.16	100.47± 13.98	0.52
POD 1	93.38± 14.17	94.47± 14.27	0.151
POD 2	93.97± 14.07	91.38± 12.13	0.056
Mean Arterial BP			
Induction	93.78± 13.18	92.88± 14.77	0.78
Incision	80.11± 15.10	77.79± 14.64	0.76
Sternotomy	77.16± 12.98	78.24± 12.88	0.045
Post Grafting	73.27± 10.41	74.71± 12.46	0.92
Post Protamine	70.68± 8.45	72.82± 10.85	0.49
ICU Arrival	79.84± 10.96	84.12± 13.78	0.96
Extubation	82.24± 10.26	85.85± 11.72	0.17
POD 1	81.54± 8.22	85.62± 10.80	0.411
POD 2	84.51± 10.73	85.91± 7.48	0.85

Table 4: Quality of Recovery (QoR-40) Dimensions and Global Score

QoR-40 Dimension		Pregabalin Group (N=37)	Placebo Group (N=34)	P value
Emotional State	Preoperative	58 ± 2	57± 3	0.07
	Postoperative	55 ± 4	52 ± 3	0.005*
Physical Comfort	Preoperative	43 ± 2	42 ± 2	0.07
	Postoperative	42 ± 3	40 ± 3	0.04*
Psychological Support	Preoperative	24± 1	24 ±1	0.11
	Postoperative	13 ± 5	12 ± 3	0.34
Physical Independence	Preoperative	35 ± 1	34 ± 1	0.61
	Postoperative	40 ± 1	40 ± 1	0.61
Pain	Preoperative	34±1	33 ± 2	0.62
	Postoperative	27 ± 2	22 ± 2	0.02*
Global QoR 40 Scores	Preoperative	194± 4	193± 4	0.12
	Postoperative	177 ± 9	170 ± 9	0.002*

*= Statistically significant.