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EFFECTS OF PREGABALIN ON POSTOPERATIVE PAIN AND AGITATION FOLLOWING CORONARY ARTERY BYPASS GRAFTING: RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Background: Postoperative pain and agitation are common and distressing complications after open heart surgery. Pregabalin is an anticonvulsant agent which reduce anxiety and some type of pain such as neuropathic pain and has anti-spastic effects. The use of this medication for controlling of postoperative pain and agitation was recently suggested. This study aimed to assess the effects of pregabalin on agitation and pain after Coronary Artery Bypass Grafting (CABG).
Methods: A total of 94 patients candidate for CABG were randomly assigned to receive placebo or pregabalin at a dose of 150 mg two hours before surgery and also 75 mg at first, second and third days after operation twice daily at 9 am and 9 pm(47 patients in each group). Two hours after drug administration in postoperative days, the patient's degree of agitation was determined using the Richmond agitation sedation scale (RASS), and pain severity was determined using the visual analogue scale (VAS) score.
Results: We found no difference between the groups at different study time points including before surgery, immediately after operation, as well as days 1, 2, and 3 after operation. There was also no difference in pulmonary functional parameters and arterial blood gas analysis between pregabalin and placebo groups at the study time points, except for PCO2 that was higher in pregabalin group at second and third days of operation. We found no difference in mean pain scores (VAS) and agitation scale (RASS) between the two groups. No difference was seen in the amount of analgesic drugs used between the two groups at different time points.
Conclusion: We found that use of pregabalin had no significant effect on relieving of post-CABG pain severity and level of postoperative agitation.

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Introduction

Almost all patients who undergo major surgeries need to plan proper strategies for relieving postoperative pain and agitation. In this regard, it is strongly recommended to monitor patients continuously after surgeries especially after admission to intensive care units (ICU) for controlling and minimizing pain and agitation [1, 2]. Both pharmacologic (opioids) and non-pharmacologic (relaxation) interventions are now commonly administered to alleviate postoperative pain [3, 4]. In some major surgeries such as open heart surgeries, a combination of both pain relieving strategies should be considered because of potentially painful nature of these surgeries [5]. To relieve pain following cardiac surgeries, administration of opioids plus epidural anesthesia/analgesia is first choice [6]. Moreover, because of adverse effects of agitation on prolonging hospital and ICU stay as well as prolonging mechanical ventilation, lowering agitation by light sedation is also recommended [7]. Also due to high incidence of post sternotomy chronic pain syndrome after coronary artery bypass grafting (CABG), severe pain and agitation which is a common postoperative finding should be relieved and lowered by the recommended approaches [8]. Beside some commonly used anesthetic and analgesic agents, several anticonvulsant and spasmolytic drugs have been shown to be useful for postoperative pain relief and agitation control. In this context, the beneficial effects of pregabalin as a new generation of anticonvulsant drugs and analogue of the neurotransmitter gamma-aminobutyric acid (GABA) on neuropathic

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pain and anxiety disorders have been identified. Also, the salutary effects of pregabalin on clinical conditions with chronic pains including post-herpetic neuralgia, inflammatory pains, pain related to malignancies, diabetic neuropathy, trigeminal neuralgia, and severe headaches have been also revealed [9,10].

In some recent trials, the efficacy of pregabalin on relieving postoperative acute pain has been shown [11, 12]. Also, due to its beneficial effects as anti-anxiety and anti-spastic effects related to its anxiolytic and analgesic properties, the use of this medication on assuaging postoperative agitation is also suggested [13]. Hence, in this study we aimed to assess the beneficial effects of pregabalin on agitation and pain after CABG.

Materials and Methods

This double-blinded, randomized, placebo controlled, prospective clinical trial was ethically approved by the Review Board of the Shiraz University of Medical Sciences. The purpose and protocols of the trial were explained to patients in detail prior to CABG surgery and informed consents were obtained from all participants. A minimum sample size of 47 patients in each group was determined to be sufficient to detect a 25% difference in requiring analgesics after surgery between study groups, assuming a power of 80% and a significance level of 5%.

Obese patients (body mass index > 35 kg/m^2), and patients with history of renal failure (serum creatinine level > 1.5 mg/dl), left ventricular dysfunction (left ventricular ejection fraction < 35%), chronic alcoholism, opium addiction, history of epileptic seizure, recent use of gabapentinoids, history of diabetes, uncontrolled hypertension, hepatic dysfunction, known sensitivity to pregabalin, redo surgery and reoperation for control of bleeding during study period, re-intubation during three days of surgery, and death within the first three days of operation were all excluded. Using block randomization method, the participants were assigned into two groups (47 patients in each group) receiving either placebo or pregabalin at a dose of 150 mg two hours before surgery and also 75 mg on first, second and third days after operation twice daily at 9 am and 9 pm. The placebo capsules were completely similar to the drug capsules but filled with starch. All patients were premedicated by midazolam (0.1 mg/kg), fentanyl (8-10 μg/kg), and morphine (0.1 mg/kg). The patients were then anesthetized using thiopental (2.5 mg/kg) and pancuronium (0.12 mg/kg). Intravenous nitroglycerine, ephedrine, and epinephrine were also considered for controlling blood pressure. Heparin was also used to achieve ACT > 480 before cardiopulmonary bypass (CPB). During CPB, blood flow was set as 2.4 to 2.8 Lit/min/m^2. With administration of vasodilators or vasopressors the hemodynamic parameters were maintained as mean blood pressure of 50 to 90 mmHg. Also serum hematocrit level of 21% to 27%, body temperature of 32 to 34°C, and blood sugar of 80 to 120 mg/dl were maintained during CPB. After completing CPB, the effect of heparin was reversed by protamine and the patient was transferred to cardiac surgery ICU. The administration of pregabalin and placebo was repeated at 1, 2, and 3 days postoperatively. Two hours after administration of each dose of drug at first, second and third postoperative days, the patient's degree of agitation was determined using the Richmond agitation sedation scale (RASS), as well as severity of pain was determined using the visual analogue scale (VAS) score.

The RASS was scored as +4 for COMBATIVE (Combative, violent, immediate danger to staff), +3 for VERY AGITATED (Pulls to remove tubes or catheters; aggressive), +2 for AGITATED (Frequent non-purposeful movement, fights ventilator), +1 for RESTLESS (Anxious, apprehensive, movements not aggressive), 0 for ALERT & CALM (Spontaneously pays attention to caregiver), -1 for DROWSY (Not fully alert, but has sustained awakening to voice, -2 for LIGHT SEDATION (Briefly awakens to voice, -4 for DEEP SEDATION (No response to voice, but movement or eye opening to physical stimulation), and -5 for UNAROUSABLE (No response to voice or physical stimulation). In addition to administration of those drugs for relieving pain (in VAS ≥ 45 mm), analgesics (including meperidine, apotel, morphine, or diclofenac suppository) were also used and total dose of each drug was also recorded for two group. The trained personnel who were responsible for taking the drugs or assessed the patients using RASS or VAS were uninformed of the method of randomization patients groups.

For statistical analysis, Kolmogorov-Smirnov test was used to check normality of data. Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using one-way analysis of t test and/or non-parametric Mann-Whitney test whenever the data did not appear to have normal distribution. Categorical variables were compared using Chi-square test or Fisher's exact test. For the statistical analysis, the statistical software SPSS version 21.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

In our study, 175 patients candidates for CABG surgery were screened of which 53 patients were not included into the study because of definitive exclusion criteria (26 opium user, 10 insulin dependent diabetics, 9 with renal failure, 3 with uncontrolled hypertension, 2 with left ventricular dysfunction, 2 with chronic hepatic dysfunction, and 1 with obesity). Also, 15 patients in pregabalin group (11 with raised serum creatinine > 1.5 mg/dl and 4 because of prolong intubation) and 10 patients in the placebo group (6 with raised serum creatinine > 1.5 mg/dl and 4 due to remaining intubated) were excluded from the study. In total, 43 patients received pregabalin and 54 received placebo.

The demographic data and some baseline parameter are seen in Table 1. two groups were similar regarding to male gender , mean CPB time and extubation time. However those who received pregabalin were older than the placebo group and had lower mean BMI value.

Comparing serum biochemical markers and hemodynamic indices between pregabalin and placebo groups showed no difference at different study time points including before surgery, immediately after operation, as well as 1, 2, and 3 days after operation (Table 2). There was also no difference in pulmonary functional parameters and also arterial blood gas analysis between pregabalin and placebo groups at the study time points, except for PCO2 that was higher in pregabalin group at second and third days of operation (Table 3).

We found no difference in mean pain severity scores (VAS) between pregabalin and placebo groups (Table 4). Also, the agitation scores (RASS) were not significantly different between the study groups (Table 5). Assessing trend of the changes in pain severity score in the two groups (figure 1) by the repeated measure ANOVA test showed no difference between pregabalin and placebo groups (p = 0.506). There was also no difference in trend of the changes in agitation score between the groups (figure 2) (P=0.682). Regarding the number of analgesic drug used postoperatively, we revealed no difference in the number of drug used between the two groups that 8.6% of patients in pregabalin group and 4.6% in placebo group received more than two analgesic drug (P=0.633). Also, the mean number of analgesic drugs prescribed at first day of operation was 1.09 in pregabalin group and 1.41 in placebo group with no statistically significant difference (P=0.121). There was also no difference between the two groups in the number of analgesic drugs used at second days (P=0.468) and third days (P=0.384) of operation. In both groups, the most common analgesic administered was meperidine followed by apotel, diclofenac suppository and morphine.

Table 1. Demographic data and baseline parameter in two study groups.

Group parameter	Pregabalin group (Mean +-Std.)	Placebo group (Mean +-Std.)	p-value
Age(years)	64.62±12.31 yrs	60.03±10.28 yrs	P=0.026
Male gender(percent)	58.6%	58.5%,	P=0.986
BMI(body mass index)	24.40 ± 3.47 kg/m^2	26.23 ± 4.05 kg/m^2	P=0.008
CPB time	1.01±0.43 hrs	0.98±0.41 h	P=0.653
Extubation time	13.52±3.46 hrs	13.35±3.35	P=0.653

Table 2. Hemodynamic parameters and biochemical indices in Pregabalin and Placebo groups

Parameter	Before surgery	Immediately after surgery	One day after surgery	Two days after surgery	Three days after surgery
SBP					
Pregabalin	130.78 ± 15.27	110.81 ± 15.86	120.60 ± 14.18	121.85 ± 15.13	121.57 ± 14.72
Placebo	128.28 ± 26.18	114.73 ± 18.14	120.83 ± 18.32	119.12 ± 13.74	118.22 ± 19.08
p-value	0.527	0.208	0.941	0.339	0.340
DBP					
Pregabalin	80.93 ± 10.52	61.67 ± 11.10	66.96 ± 14.54	71.11 ± 11.33	74.18 ± 13.00
Placebo	79.61 ± 11.42	62.64 ± 12.15	68.83 ± 12.16	71.12 ± 9.92	73.49 ± 8.57
p-value	0.509	0.648	0.451	0.995	0.752
HR					
Pregabalin	86.48 ± 8.97	96.75 ± 12.53	91.65 ± 10.80	93.09 ± 14.69	93.39 ± 8.34
Placebo	84.43 ± 8.85	96.11 ± 14.54	93.16 ± 11.52	93.82 ± 11.64	93.62 ± 12.21
p-value	0.208	0.795	0.468	0.775	0.915
RBC count					
Pregabalin	4.86 ± 1.39	3.86 ± 0.51	4.09 ± 0.49	3.86 ± 0.51	4.04 ± 0.44
Placebo	4.89 ± 0.57	3.96 ± 0.48	4.12 ± 0.50	4.05 ± 0.45	4.06 ± 0.43
p-value	0.849	0.293	0.822	0.053	0.863
WBC count					
Pregabalin	7.72 ± 1.98	15.11 ± 4.36	11.72 ± 3.24	12.74 ± 3.39	12.41 ± 3.45
Placebo	7.50 ± 2.21	14.06 ± 5.63	11.46 ± 3.59	12.05 ± 3.59	11.61 ± 3.21
p-value	0.561	0.256	0.683	0.324	0.224
PLT count					
Pregabalin	249.79 ± 75.94	156.76 ± 64.14	162.87 ± 68.72	134.35 ± 42.30	145.24 ± 43.65

Placebo	241.19 ± 78.49	149.12 ± 39.87	151.50 ± 47.40	133.76 ± 42.67	140.41 ± 38.73
p-value	0.540	0.427	0.295	0.944	0.568
Serum HB					
Pregabalin	13.27 ± 1.86	10.30 ± 1.30	11.13 ± 1.07	10.48 ± 0.98	10.68 ± 0.90
Placebo	13.54 ± 1.68	10.33 ± 1.15	10.99 ± 1.14	10.78 ± 1.06	10.89 ± 0.96
p-value	0.404	0.865	0.509	0.134	0.286
Serum Cr					
Pregabalin	1.02 ± 0.19	1.01 ± 0.19	1.21 ± 0.44	1.05 ± 0.35	1.03 ± 0.23
Placebo	1.03 ± 0.25	0.95 ± 0.26	1.07 ± 0.32	0.99 ± 0.37	1.08 ± 0.98
p-value	0.817	0.162	0.053	0.369	0.723
Serum BUN					
Pregabalin	17.43 ± 6.23	16.71 ± 5.97	21.33 ± 8.00	21.30 ± 10.25	19.11 ± 6.24
Placebo	17.35 ± 6.60	14.20 ± 5.25	17.90 ± 7.24	18.22 ± 7.97	16.87 ± 5.50
p-value	0.940	0.015	0.017	0.088	0.069
SaO2					
Pregabalin	93.33 ± 1.53	97.81 ± 2.00	95.02 ± 3.28	93.09 ± 3.49	94.62 ± 2.21
Placebo	94.40 ± 2.50	97.79 ± 1.59	94.13 ± 5.18	94.15 ± 3.45	93.81 ± 2.97
p-value	0.506	0.975	0.124	0.136	0.216

Table 3. Pulmonary functional indices and arterial blood gas analysis in Pregabalin and Placebo groups

Parameter	Immediately after surgery	One day after surgery	Two days after surgery	Three days after surgery
PaO2				
Pregabalin	195.41 ± 79.65	87.96 ± 22.03	72.78 ± 18.24	58.18 ± 23.57
Placebo	180.52 ± 72.25	84.26 ± 25.05	74.63 ± 14.00	70.63 ± 13.58
p-value	0.283	0.403	0.560	0.178
PH				
Pregabalin	7.27 ± 0.40	7.38 ± 0.08	7.37 ± 0.43	7.42 ± 0.03
Placebo	7.34 ± 0.05	7.39 ± 0.04	7.44 ± 0.05	6.71 ± 2.35
p-value	0.222	0.553	0.174	0.405
PaCO2				
Pregabalin	34.93 ± 5.55	36.24 ± 5.97	37.58 ± 5.35	41.52 ± 9.28
Placebo	35.24 ± 5.43	36.70 ± 4.26	35.51 ± 4.76	34.76 ± 3.59
p-value	0.761	0.628	0.038	0.049
HCO3				
Pregabalin	18.59 ± 2.51	20.61 ± 4.46	25.32 ± 2.52	27.40 ± 4.28
Placebo	18.81 ± 2.84	21.80 ± 2.63	26.67 ± 9.96	24.05 ± 3.97
p-value	0.655	0.077	0.373	0.105

Table 4. Pain severity score on VAS in Pregabalin and Placebo groups

	group	N	Mean	Std. Deviation	Std. Error Mean	p-value
VAS1	Pregabalin	52	35.1923	21.12896	2.93006	0.824
	Placebo	61	34.2295	24.16705	3.09427	
VAS2	Pregabalin	50	29.5400	14.31883	2.02499	0.522
	Placebo	60	31.8833	22.22084	2.86870	
VAS3	Pregabalin	47	23.0638	15.22070	2.22017	0.189
	Placebo	59	18.8814	16.90346	2.20064	
VAS4	Pregabalin	45	20.0000	13.74938	2.04964	0.624

	Placebo	57	18.5789	14.34766	1.90039	
VAS5	Pregabalin	43	12.7674	12.45532	1.89942	0.562
	Placebo	55	11.3273	11.89935	1.60451	
VAS6	Pregabalin	43	10.8837	11.04150	1.68381	0.222
	Placebo	54	8.2963	9.67711	1.31689	

Table 5. Agitation scores on RASS in Pregabalin and Placebo groups

	Group	N	Mean	Std. Deviation	Std. Error Mean	p-value
RASS1	Pregabalin	52	.0962	.60260	.08357	0.981
	Placebo	61	.0984	.39602	.05070	
RASS2	Pregabalin	49	.0612	.47470	.06781	0.551
	Placebo	60	.1333	.72408	.09348	
RASS3	Pregabalin	48	.0417	.28868	.04167	0.875
	Placebo	60	.0333	.25820	.03333	
RASS4	Pregabalin	44	-.0227	.26313	.03967	0.945
	Placebo	57	-.0175	.44285	.05866	
RASS5	Pregabalin	43	.0465	.21308	.03249	0.070
	Placebo	55	-.0182	.13484	.01818	
RASS6	Pregabalin	43	.0233	.15250	.02326	0.528
	Placebo	55	.0000	.19245	.02595	

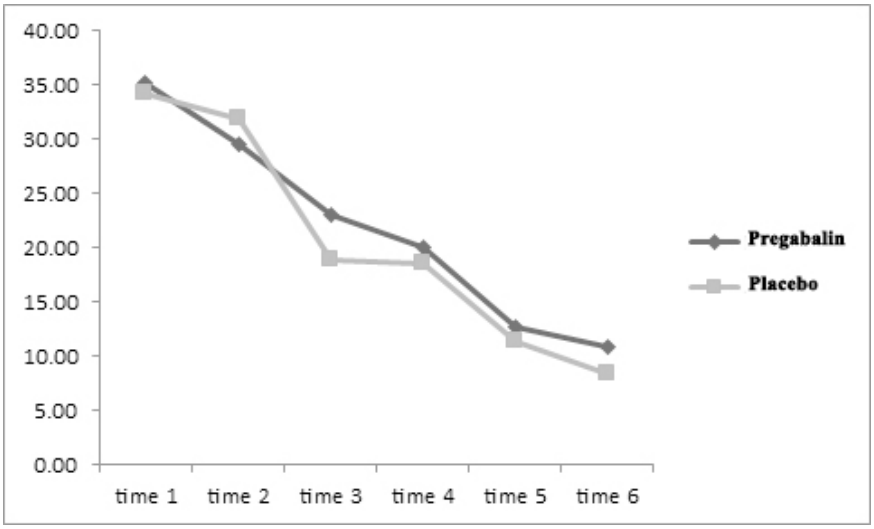

Figure 1. Trend of the changes in pain severity score on VAS in Pregabalin and Placebo groups

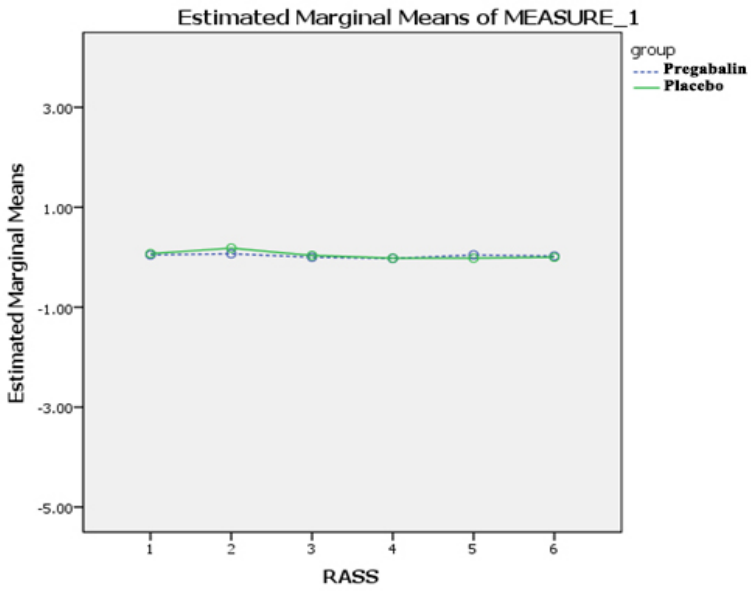

Figure 2. Trend of the changes in Agitation scores on RASS in Pregabalin and Placebo groups

Discussion

We aimed to investigate the efficacy of pregabalin on lowering postoperative pain severity as well as level of postoperative agitation; however we could not demonstrate its efficacy for lowering pain and agitation early after CABG as a major surgery. On the other hand, it seems that the consumption of pregabalin may not be effective in relieving acute postoperative pain or agitation.

In line with our finding, it has been previously revealed that pregabalin is not efficacious in relieving acute pain. Some trials also tried to assess the efficacy of this drug to lower acute postoperative pain, but overally no effect of the drug on post-surgical pain was indicated [13,14]. Furthermore, although we could not show lower need to analgesics and number of dosages, some trials demonstrated requiring fewer dosages of morphine and opioids after surgery. More interestingly, some other trials especially on older populations indicated lower level of postoperative pain, three months after surgery, but without significant effect on severity of acute postoperative pain [13-15]. Although beneficial effects of pregabalin on post-CABG pain and agitation remain uncertain, this efficacy was exclusively assessed in other types of surgeries. In a recent clinical trial by Park et al, the total amount of required fentanyl decreased significantly following pregabalin administration, but this beneficial effect was not found in other clinical parameters such as pain scores, postoperative satisfaction, headache, and vomiting postoperatively [16]. In another trial by Singla et al, no significant difference was found between pregabalin and placebo with respect to the pain intensity measure [17]. In another study by Matsutani and contrary to our observation, the pain scores, as well as sleep disturbance and incidence of neuropathic pain were significantly lower in the pregabalin group compared to placebo group in all study time points [18]. In a systematic review on 55 trials, it was shown that using pregabalin with a wide range between 100 to 300 mg could not reduce pain severity, however all doses of pregabalin tested (≤75, 100-150, and 300 mg) resulted in opioid sparing at 24 h after surgery [19]. In total, few evidence is available confirming the significant efficacy of pregabalin on relieving postoperative pain and agitation. Although our observation is in line with most previous observations, but the obtained results may be affected by some potential confounders such as small sample size, using different pain and agitation scoring systems as well as focusing on acute post-CABG pain limited to first three days after operation.

We considered a dose of 150 mg of pregabalin daily in our intervention. The effect of the different dosages of drug on pain severity and agitation level achieved contradictory results. Although some studies show drug efficacy independent to its dosage (Mishriky), some trials demonstrate higher dose such as the dose of 600 mg as the optimal preemptive dose for postoperative analgesia. It has been also found that higher doses of pregabalin is not accompanied with higher efficacy, but may leading higher rate of side effects [20]. Thus, it seems that we used a dose of drug lower than the optimal level that may partially explain lack of clinical efficacy of drug on relieving pain or agitation after surgery.

In summary, according to our findings the use of pregabalin had no significant result in relieving post-CABG pain severity and level of postoperative agitation. It seems that the obtained result may be influenced by the drug dosage, lower that the optimal dose and thus testing the results with different drug dosages is recommended.

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