THE EFFICACY OF PREGABALIN AS A PREMEDICANT IN ATTENUATING NEUROENDOCRINE STRESS RESPONSE DURING GENERAL ANAESTHESIA IN ELECTIVE SURGERIES: A PROSPECTIVE RANDOMISED PLACEBO CONTROLLED STUDY

Bhavani Muthukrishnan[1], Murugan Thalaippan[2]

[1]Senior Resident, Department of Anaesthesiology, Kilpauk Medical College.
[2]Professor, Department of Anaesthesiology, Kilpauk Medical College.

ABSTRACT

BACKGROUND

The stress response to surgery is characterised by increased secretion of pituitary hormones and activation of the sympathetic nervous system**.** The changes triggered by the stress response are short-lived and well tolerated by normal healthy patients belonging to ASA 1 and 2. In patients with other comorbidities like myocardial ischaemia, renal insufficiency, uncontrolled diabetes, liver disease and cerebrovascular diseases, these changes can be life threatening. The recognition of the factors which initiate the stress response can be considered for modification in the preoperative period itself. Various anaesthetic techniques and pain management strategies have been put into use to control the stress response.

AIM

To study the rise in serum cortisol levels during surgery after administering oral pregabalin as a premedicant.

SETTINGS AND DESIGN

A Prospective Randomised Placebo Controlled Study.

MATERIALS AND METHODS

All consented patients were aged between 18 and 50 years belonging to ASA 1 & 2 undergoing elective surgical procedures under general anaesthesia of duration between 30 minutes and 180 minutes. Group A received oral placebo, Group B oral pregabalin 150 mg 60-90 minutes before surgery with sips of water. They were randomly allocated to a particular group using computer generated numbers. The ward staff nurse administered the drug kept in sealed envelopes. Both the patients and the person administering anaesthesia were unaware of the group.

STATISTICAL ANALYSIS

The results were analysed using SPSS Version 17 software with the help of the statistician. The students' paired t-test was used to compare the mean change in the cortisol levels in the two groups.

RESULTS

There was a significant [$p < 0.01$] reduction in the intraoperative cortisol levels after premedication with pregabalin. There was an increase in serum cortisol levels after extubation in both the groups which was statistically significant ($p < 0.01$).

CONCLUSION

Pregabalin in the dose of 150 mg given per orally one hour before elective surgeries can attenuate the neuroendocrine stress response due to induction and intubation. Better surgical skills and techniques have got a major role in attenuating neuroendocrine stress response more than the conventional anaesthetic interventions.

KEYWORDS

Premedication, Oral Pregabalin, General Anaesthesia, Attenuation of Stress Hormones, Haemodynamic Parameters.

MeSHTerms

Serum Cortisol levels, Surgical stress response, Pregabalin.

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Corresponding Author:
Dr. Bhavani Muthukrishnan,
Senior Resident, Department of Anaesthesiology,
Kilpauk Medical College.
E-mail: mbaval75@yahoo.co.in
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INTRODUCTION: The stress response to surgery is characterised by increased secretion of pituitary hormones and activation of the sympathetic nervous system.[1] The changes in pituitary secretion have secondary effects on hormone secretion from various organs. For example, release of corticotropin from the pituitary stimulates cortisol secretion from the adrenal cortex. Arginine vasopressin which is secreted from the posterior pituitary has effects on the kidney. In the pancreas, glucagon is released and insulin secretion may be diminished. The overall metabolic effect of the hormonal changes is increased catabolism which mobilises substrates to provide energy sources, and a mechanism to retain salt and water to maintain fluid volume and cardiovascular homeostasis.[2]

The changes triggered by the stress response are short-lived and well tolerated by normal healthy patients belonging to ASA 1 and 2. In patients with other comorbidities like myocardial ischaemia, renal insufficiency, uncontrolled diabetes, liver disease and cerebrovascular diseases, these changes can be life threatening. A number of experiments have been carried out to associate various events in anaesthesia to the development of stress response.[3]

Thus, the importance of attenuating the stress response is well evident and this study aims to compare oral Pregabalin with a placebo in attenuating the neurohumoral stress response.

AIMS AND OBJECTIVES:

Primary Objective: To study the rise in serum cortisol levels during surgery[4,5] after administering oral pregabalin as a premedicant.

Secondary Objective: To evaluate the changes in plasma glucose and the haemodynamic parameters like heart rate and blood pressure.

The Stress Response and the Stress Hormones: Hypoxia, hypotension, profound hypothermia, induction, intubation, extubation, light plane of anaesthesia, unneutralised pain, surgical manipulation, wound healing and inflammation are the stimuli that trigger the stress response.

The stimuli travel to the limbic system and from there to the posterior hypothalamus. The posterior hypothalamus controls the release of various hormones from pituitary like arginine vasopressin, adrenocorticotropic hormone and aldosterone. They in turn release cortisol and catecholamine through the stimulation of the adrenals and the autonomic nervous system. This causes rise in heart rate, blood pressure and glucose levels.[6]

Increase in cardiac output occurs due to vasoconstriction of the peripheral and splanchnic vessels while vasodilation occurs in coronary and cerebral vessels. Increase in heart rate, blood pressure, myocardial contractility increases oxygen demand. The respiratory rate increases. Sodium and water retention occurs resulting in decreased urinary output. Immunosuppression predisposes to infection. Substrate mobilisation causes protein breakdown and hyperglycaemia.

More recently antiepileptic drugs have been used for the treatment of acute postoperative pain and to reduce the postoperative analgesic requirements. Pregabalin is effective in preventing neuropathic pain. It is well absorbed after oral administration and well tolerated with limited side effects with any significant drug interactions. Pregabalin undergoes negligible hepatic metabolism and is eliminated by renal excretion.

MATERIALS AND METHODS:

Inclusion Criteria: All consented patients aged between 18 and 50 years belonging to ASA 1 undergoing elective surgical procedures under general anaesthesia of duration between 30 minutes and 180 minutes.

Exclusion Criteria: All those with pre-existing cardiac disease, hypertension, diabetes, asthma, hepatic and renal dysfunction will be excluded. All those with anticipated difficult intubation, obesity, pregnant patients, patients on antihypertensives, antidepressants and anticonvulsants will be excluded. Those with baseline abnormalities in the lab values will also be excluded.

Procedure: After getting the Institutional Ethical Committee approval, all consented patients, fulfilling the inclusion criteria were selected and divided into two groups. Group A received oral placebo, Group B oral pregabalin 150 mg 60-90 minutes before surgery with sips of water. They were randomly allocated to a particular group using computer generated numbers. The ward staff nurse administered the drug kept in sealed envelopes. For uniformity, all premedicated patients were assigned as first case in the operative list. Both the patients and the person administering anaesthesia were unaware of the group. The details of the study were explained to the participants in their own language and informed consent was obtained on the day prior to surgery.

In the preoperative ward, selected patients' first blood sample was collected around 8.00 a.m., since based on the circadian rhythm the cortisol levels come to a peak level around 8' o clock in the morning[6]. For most of the cases, blood was drawn for grouping and crossmatch so along with that an extra 2 mL was drawn. After administration of the drug one hour before surgery, patients' vitals were monitored and given oxygen supplementation if SpO2 falls below 95%. They were brought to the operation theatre in a stretcher accompanied by medical/paramedical personnel. Inside the theatre before induction of anaesthesia, second blood sample was taken after putting an intravenous cannula and crystalloid infusion of 6-8 mL/kg/hr. was started.

Standardised anaesthesia technique using Glycopyrrolate 0.2 mg (2 mcg/kg), Inj. fentanyl 2 mcg/kg, Inj. midazolam 1 mg, Inj. Thiopentone 5 mg/kg, Vecuronium 0.15 mg/kg and Sevoflurane/ N_2O:O_2 was done.

Unanticipated difficult intubation cases (more than one attempt or duration> 45 secs.) were excluded. Within fifteen minutes after intubation, third blood sample was taken. All patients were given 15 mg/kg of intravenous paracetamol one hour after induction. At the end of surgery, all patients received inj. Glycopyrrolate 10 mcg/kg and inj. Neostigmine 40-70 mcg/kg was used to reverse residual neuromuscular block and extubated. Immediately within fifteen minutes after extubation, fourth blood sample was taken. All patients were observed in the recovery room before shifting to the postoperative ward. Along with serum cortisol, plasma glucose and serum prolactin were also measured in the fourth sample.

During the course of the surgery, blood pressure and pulse rate were noted down in the anaesthesia management chart maintained by the person giving anaesthesia. On the first postoperative day, morning sample was taken at 8.00 a.m. when blood was collected for routine investigations.

Sample Analysis: All the blood samples were centrifuged immediately and stored at -20$^{0.}$ C till the testing was done. Samples for blood glucose were collected in fluoride tubes and tested as early as possible.

Blood Samples taken for Analysis:
Serum Cortisol[7,8,9]**:** Baseline, After Premedication, Post intubation, Post extubation, Postoperative sample after 24 hrs.
Blood Glucose: Preoperative and Postoperative.

STATISTICAL ANALYSIS: After consulting the statistician, the sample size was set at 80 patients. Initial pilot observation showed a 10% difference between the control and the premedicated group. This study was designed to find out the difference between the two groups: T. Pregabalin 150 mg and the placebo group. After thorough review of previous studies,[7,8,9,10] approximately 40 patients including 5% for missing values were included in each group in order to ensure a power of 80% which would permit a type 1 error of ∝ =0.05. The results were analysed using SPSS Version 17 software with the help of the statistician.

Normality was checked using Kolmogorov-Smirnov test and it resulted in a p> 0.005 for almost all the variables which implies that the data are normally distributed. The students paired t-test was used to compare the mean change in the cortisol levels in the two groups. Categorical variables were analysed using Chi square test. Values that were not normally distributed or when the mean value was less than two times the standard deviation, were analysed with non-parametric statistical methods (2-tailed Wilcoxon signed rank tests). All results were presented as means ± standard deviation. A p value <0.05 was considered as statistically significant.

Group	Placebo N=37	Pregabalin N= 48
Age (years)	33.45 ± 11.92	31.27± 11.17
Sex (M:F)	16:21	24:24
Duration of surgery (Hrs.)	2.17 ± 0.77	2.11± 0.62

Table 1: Population Characteristics

	Placebo mean±sd (mcg/dL)	p value	Pregabalin mean±sd (mcg/dL)	p value
C1:C2	14.76±4.4: 11.56±6.0	p=.002	14.97± 7.16: 11.59± 7.8	p=.014
C1:C3	14.76±4.4: 13.52±6.7	p=.019	14.97±7.16: 13.6±6.88	p=.021
C1:C4	14.76±4.4: 23.26±10.3	p<.001	14.97±7.16: 25.71±18.3	p<.001
C1:C5	14.76±4.4: 12.42±3.2	p<.001	14.97±7.16: 11.63±5.84	p=.001

Table 2: Cortisol Levels in Placebo and Pregabalin Group

C1: baseline cortisol levels, C2: after premedication, C3: after intubation, C4: after extubation, C5: after 24 hours.

Baseline cortisol values were comparable in both the groups. All the other values were compared with the respective baseline value.

There was a significant reduction in the cortisol levels after premedication with pregabalin (control-p=0.002/ Pregabalin-p=0.014). There was significant reduction in the baseline cortisol level and the post-intubation cortisol levels p <0.01 in pregabalin group. There was an increase in serum cortisol levels after extubation in both the groups which was statistically significant (p < 0.01). Though the mean value after extubation was slightly greater in the placebo group than the pregabalin group, the serum cortisol levels returned to baseline values within twenty four hours after surgery in both the groups.

Group	Preoperative mg/dL	Postoperative mg/dL	
Placebo	87±12.38	124.6±37	p=ns
Pregabalin	88.64±13.62 (p=.001)	126.08±33 (p=.007)	

Table 3: Blood Glucose

Both the groups did not have significant reduction in the blood glucose levels.

HAEMODYNAMIC VARIABLES:

Group	Baseline Rate/Minute	After Premedication Rate/Minute	After Intubation Rate/Minute	After Extubation Rate/Minute	After 24 hours Rate/Minute
Placebo	74.59±8.421	73.59±7.11 (ns)	87.65±128 (p<.001)	83.19±10.3 (p<.001)	91.29±14.6 (ns)
Pregabalin	78.17±10.82	75.21±8.27 (p=.002)	85±12.41 (p=.002)	84.42±11.29 (p=.002)	90.21±12.4 (ns)

Table 4: Heart Rate

Group	Baseline mm of Hg	After Premedication mm of Hg	After Intubation mm of Hg	After Extubation mm of Hg	After 24 hours mm of Hg
Placebo	114.22 ±11.74	118.27±12.47 (p=.025)	131.35±12.06 (p<.001)	132.62±10.7 (p<.001)	135.35±24.9 (ns)

Table 5: Systolic Blood Pressure

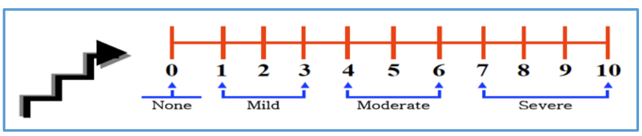
Group	Baseline mm of Hg	After Premedication mm of Hg	After Intubation mm of Hg	After Extubation mm of Hg	After 24 hours mm of Hg
Placebo	75±9.79	73.03±9.84 (ns)	81.92±10.36 (P=.001)	80.84±12.29 (p=.014)	83.18±11.7 (ns)
Pregabalin	74.31±8.60	71.48±9.75 (ns)	83.56±11.34 (p<.001)	80.85±9.20 (p=.002)	86.75±13.08 (ns)

Table 6: Diastolic Blood Pressure

In the placebo group, there was no significant decrease in heart rate and diastolic blood pressure one hour after induction though there was a slight decrease in systolic blood pressure. There was no significant reduction in the haemodynamic variables after twenty four hours.

In the Pregabalin group, there was significant decrease in heart rate but not in the blood pressure after premedication. But there was a significant decrease in the haemodynamic variables after intubation and after extubation, though there was no significant change after twenty four hours.

Postoperative Pain Score (Numerical Rating Scale): Numerical rating scale:



Postoperative pain was assessed by using the numerical rating scale. There was significant reduction in Pregabalin group (p < 0.01) than Placebo group.

Time After Extubation	0-2 hrs.	2-4 hrs.	4-6 hrs.	
Placebo	30	7	0	P<.001
Pregabalin	5	24	19	

Table 7: Postoperative Analgesic Requirement

Postoperative analgesic requirement was significantly low in the Pregabalin group. (p<.001) but in the Placebo group, most of them needed analgesics within two hours of extubation.

DISCUSSION: Our study intended to study the pattern of rise of serum cortisol in response to anaesthesia and surgery after premedicating two groups of patients, one with Placebo and another with pregabalin. Our results showed that the increase in serum cortisol was blunted by the administration of Pregabalin. This reduction was significant just before and after intubation and was not significant at the end of the surgery and extubation. The serum cortisol levels were around the baseline after twenty four hours after surgery. This finding is consistent with the study conducted by Barker et al.[7]

The degree of surgical manipulation seems to be the main causative factor in triggering the neuroendocrine stress response as Unase et al in their study quoted that 'the immunoendocrine response to surgical trauma is dependent on the surgical technique'. The finding in our study was consistent with this observation and the post extubation cortisol values were very high.

In our study, we were able to demonstrate significant reduction in the post intubation serum cortisol values thus proving that Pregabalin is a good adjuvant for smooth induction of anaesthesia.

Most of the studies done with Pregabalin in attenuating stress response compared haemodynamic parameters rather than the stress hormones. The serum cortisol levels in post extubation phase were high in both groups which needs to be further validated by more studies in future. The heart rate was controlled before induction by Pregabalin efficiently than placebo substantiates the fact that Pregabalin produces good anxiolysis. The role of Pregabalin as an anxiolytic is well showed by Baidiya et al [11], where they say that Pregabalin is effective in the treatment of generalised anxiety disorder. Pregabalin has less effect on the haemodynamic parameters so there was no statistically significant decrease in the systolic and diastolic blood pressure after premedication.

The increase in haemodynamic variables observed in the intraoperative period need not directly attribute to the neuroendocrine stress response because George et al have concluded in their study that the way in which the body responds to the increase in catecholamines is always not proportional to the catecholamine levels. They also added that hormonal estimation was more reliable than the haemodynamic responses in quantifying the stress response.

In our study, we found that Pregabalin failed to prevent increase in cortisol levels and hyperglycaemia after extubation. The stress hormones are released more in response to surgical manipulation and preoperative drugs have got little control over the stress hormones at the end of surgery. Modifying the surgical technique, minimal tissue handling, reducing the duration of surgery may be successful in alleviating the neurohumoral stress response.

Pregabalin seems to be superior in maintaining stable haemodynamics and so it scores well over placebo as a premedicant. The patients belonging to Pregabalin group were cooperative, alert, calm, in the preoperative period and a sense of well-being prevailed in the postoperative period. The requirement of analgesia was significantly delayed ($p< 0.001$) in this group in the immediate postoperative period.

CONCLUSION: From this study, it is concluded that Pregabalin in the dose of 150 mg given per orally one hour before elective surgeries can attenuate the neuroendocrine stress response due to induction and intubation.

This dose is optimal in that it doesn't cause undue preoperative and post-procedural sedation, at the same time provides efficient analgesia[12] in the early postoperative period.

Better surgical skills and techniques have got a major role in attenuating neuroendocrine stress response more than the conventional anaesthetic interventions.[13]

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