

Evaluation of Premedication with Oral Pregabalin on Attenuation of Haemodynamic Response to Laryngoscopy and Endotracheal Intubation

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Abstract

Original Research Article

General Anaesthesia with endotracheal intubation is the anaesthetic method of choice for many major and prolonged surgical interventions. The profound stress response associated with the performance of laryngoscopy and endotracheal intubation is often associated with deleterious effects in susceptible patient groups. Various drugs and methods have been studied for the attenuation of this reflex response to the procedure with varied results. The present study compared oral Pregabalin 150mg and a placebo given one hour before the procedure as premedication. The anaesthetic procedure was standardized in all the patients. Post-operative pain was managed with patient controlled analgesia with intravenous fentanyl. The rise in heart rate around the anaesthesia induction-intubation period was less in the pregabalin group compared to the placebo. Pregabalin significantly attenuated systolic, diastolic and mean blood pressures comparatively during laryngoscopy and intubation. Patients in the pregabalin group were found more sedated; however recovery profile was not found affected. Pregabalin significantly reduced post-operative fentanyl requirements. No major side effects were noted with the use of Pregabalin.

Keywords: Anaesthesia, Pregabalin, Haemodynamic, Laryngoscopy, Endotracheal.

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INTRODUCTION

Laryngoscopy and endotracheal intubation constitute the fundamental procedures done while providing general anaesthetic for major and prolonged surgical procedures. Though the sophistication of gadgets employed for these procedures has improved, the occurrence of haemodynamic response to the procedure still is a matter of concern to the attending anaesthesiologist. The stress response, largely sympathetic in origin, has often propensity to cause dangerous consequences like dysrhythmias and myocardial ischaemia [1,2].

Studies have been done with intravenous and topical agents sprayed over the glottis for their effect on blunting the stress response. There are favourable and adverse events noted with these drugs and none has been declared superior to others.

Pregabalin is a Gabapentanoid group of drug approved for use in seizures and chronic pain conditions. This drug has been proposed for its effect on stress response to laryngoscopy [3].

This study was done to evaluate the efficacy and safety of premedication with oral Pregabalin 150 mg given one hour before the procedure in attenuating the haemodynamic response to laryngoscopy and intubation. Post anaesthesia recovery profile, postoperative analgesic requirements and adverse effects of Pregabalin, if any were also studied.

METHODS

The study was approved by the Institutional Ethical Committee. The study was designed as a Prospective, randomized, double blinded comparative trial. Pilot study was done to ascertain the feasibility and to arrive at the statistically sufficient number of subjects required for the study.

Sixty patients aged 20 to 60 years of age of either sex, normotensive patients classified under ASA I or II category scheduled to undergo elective abdominal surgeries under general anaesthesia with endotracheal intubation were chosen for the study. Patients with anticipated difficult intubation with expected duration of intubation attempt of more than 30 seconds; those with seizure disorder; patients already on treatment with pregabalin or gabapentin; history of known allergy to

pregabalin; pregnant patients and those who did not give consent for participation in the study were excluded.

The patients chosen for the study were explained about the study and informed written consent was taken. Preoperatively a day before surgery patients were trained to use the visual analogue scale chart and patient controlled analgesic pump. On the night before surgery all patients were premedicated with Ranitidine 150mg and Alprazolam 0.5 mg per oral.

The patients were then randomized into two groups of 30 each, Group C and Group P. One hour before the procedure, patients in Group C received the placebo capsules and those in Group P received Pregabalin 150 mg per oral. Allocation to groups and drug administration was done by an anaesthesiologist not involved in the study. Both the investigator and the observer were blinded about the allocation of patients to groups.

The anaesthetic procedure thereafter was standardized between both the groups. On the morning of surgery all patients received Ranitidine 150 mg and Metaclopramide 10 mg intravenously one hour before procedure. Glycopyrrolate 0.2mg, Midazolam 0.04 mg/Kg and Fentanyl 2 µg/Kg were administered intravenously 5 minutes before induction. Anaesthesia was induced with Thiopentone 5 mg/Kg and intubation facilitated with Succinyl Choline 2 mg/Kg intravenously. Maintenance of Anaesthesia was done with 2% Sevoflurane in a mixture of 66% nitrous oxide in oxygen and increments of 0.02mg/Kg of Vecuronium through intravenous route. At the end of the procedure neuromuscular blockade was reversed with mixture of neostigmine 0.05mg/Kg and Glycopyrrolate 0.5 mg intravenously. Postoperative analgesia was given with Fentanyl through patient controlled analgesia (PCA) pump. A demand dose of 25 µg and a lock out interval of 15 minutes was set in the PCA pump. Visual analogue score (VAS) was done and when VAS was 4 or more additional dose of fentanyl 25 µg was given.

The following observations were made

Heart rate, Systolic, Diastolic and Mean blood pressure were recorded at baseline on arrival to the operating room, after induction, 1 minute, 3 minutes, 5 minutes and 10 minutes after laryngoscopy and intubation. Bradycardia was defined as heart rate of less than 60 beats per minute and was treated with Atropine 0.6 mg intravenously. Hypotension was defined as systolic blood pressure less than 90 mm of Hg and was treated with 200 ml bolus of intravenous crystalloid solution and Ephedrine 3 mg intravenously.

Laryngoscopy and intubation was performed by an anaesthesiologist with more than 2 years of experience in performing the procedure. The time taken for laryngoscopy and intubation was recorded and when

it exceeded the upper limit of 30 seconds, such cases were planned to be excluded from the study. In our case, there were no such cases.

Sedation level was assessed using Ramsay Sedation Scale. Recordings were made at baseline before drug administration and one hour after giving the drug. In the post-operative period sedation levels were assessed on admission to post anaesthesia care unit, 1 hour, 2 hours, 4 hours, 8 hours and 12 hours thereafter.

The characteristics of recovery from general anaesthesia, events like nausea, vomiting, shivering, bradycardia, hypotension (as defined above) and respiratory depression (defined as respiratory rate less than 10/minute) were observed for and recorded.

The total dose of fentanyl consumed in the postoperative period over the first 12 hours was calculated and analysed. The frequency of additional doses required was also compared between groups.

RESULTS

The data collected from the observations during the study were tabulated in Microsoft Excel and SPSS software was used for statistical analysis. Student t-test and Chi-square test were used as appropriate. P value of less than 0.05 was taken as significant and less than 0.01 was considered as highly significant.

The demographic profile with respect to age, sex and weight and ASA physical status were comparable between the two groups. The mean duration of surgery was comparable and the duration of laryngoscopy was also comparable between the study groups.

Analysis of the heart rate between the groups showed no difference at baseline, before and after anaesthesia induction. Heart rate rose at 1st, 3rd and 5th minutes following laryngoscopy and intubation. The rise in heart rate was significantly less in Group P compared to Group C. Heart rate returned to baseline in both the groups in the recordings done after 5 minutes.

No significant difference was noted in the blood pressure readings (systolic, diastolic and mean blood pressures) taken at baseline, at induction and post induction. Systolic and Diastolic blood pressures were significantly attenuated in Group P immediately after intubation, at 1st minute and 3 minutes after intubation compared to Group C (Tables 1 &2). There was a highly significant attenuation of mean blood pressure noted in Group P than Group C (Table 3).

In general, patients in Group P were sedated with brisk response to stimulus (Ramsay Sedation Scale). The mean sedation score was significantly higher in Group P than in Group C after one hour of study drug administration. The difference in sedation scores on

admission to the PACU, at 1st hour and 2nd hour were highly significant between the groups. Patients in Group P were found more sedated (Table 4). However, this did not interfere with application of VAS for pain assessment.

Recovery profile after general anaesthesia and occurrence of events like nausea and vomiting were comparable between both the groups. No further adverse events were noted in patients of either group (Table 5).

In Group P, 4 patients required one additional dose (over the mandatory demand doses set in the PCA pump); whereas in Group C 13 patients needed one additional dose and 1 patient needed 2 additional doses of fentanyl to keep VAS under 4. This was found to be statistically significant. Moreover, the total fentanyl consumption in the first 12 hours of surgery was 204 µg in Group P compared to 315 µg in Group C and this difference was highly significant on statistical testing.

The mean VAS for pain at rest evaluated at baseline at 1 hour, 4 hours and 8 hours after admission in PACU were comparable between both the groups whereas, VAS score at 2 hours and 12 hours were significant lower in Group P.

DISCUSSION

This study evaluated the effectiveness of premedication with a single dose of pregabalin administered orally one hour before induction on attenuation of hemodynamic stress response to laryngoscopy and intubation. The possibility of pre-emptive effect on post-operative patient controlled analgesia with fentanyl was also evaluated.

Reflex sympathoadrenal response with increase in serum catecholamines has been postulated as the mechanism for the stress response during laryngoscopy and intubation [3]. Studies have quoted increased incidence of myocardial ischaemia, infarction and dysrhythmias particularly in hypertensive patients and the elderly in whom the response is exaggerated [4]. Drugs like lidocaine, fentanyl and remifentanyl have been tried in the attenuation of this troublesome laryngoscopic stress response with varying effects on the heart rate [5].

Gabapentin was the first drug in its group of $\alpha 2\delta$ subunit of neuronal calcium channels to be studied for its effect on attenuation of laryngoscopic stress response. Fassoulaki found that 1600 mg of Gabapentin given in a serial of four doses attenuated the pressor response but not tachycardia during intubation [6].

Pregabalin in a similar drug touted to have better pharmacological profile with predictable onset time and bioavailability. Several dose finding studies conducted to evaluate the right dose of pregabalin

premedication for attenuation of laryngoscopic stress response have shown 150 mg to be the best dose [7-9].

During all studies analyzing the effect of a particular agent on the pressor response to laryngoscopy and intubation, the anaesthetic technique employed plays a confounding role. In the present study the combination of Thiopentone and Succinyl choline was used for anaesthetic induction and hence tachycardia was observed in both the groups. However the increase in heart rate was comparatively lesser in the pregabalin group.

The exact mechanism by which Pregabalin attenuates the pressor response is still unknown. Robert D Todd had done a study of the effects of gabapentin on adrenal cells in a primary culture of bovine adrenal chromaffin cell model. He observed that gabapentin reduced release of catecholamine from adrenal chromaffin cells without altering its contents. He also observed that the drug gabapentin did not restrict the entry of calcium into cells but calcium was less effective in causing vesicle fusion [10].

In such studies assessing the pressor response to laryngoscopy, the duration of laryngoscopy and the grade of laryngoscopy can skew the results of the study. This factor was overcome by standardizing the person performing the laryngoscopy and an experience of at least two years in performing laryngoscopy was made mandatory.

Pregabalin produced a higher level of sedation in comparison to the placebo however it did not delay the recovery from anaesthesia. Of course, the level of preoperative sedation could have affected the randomization process.

In this study we used patient controlled analgesia with intravenous fentanyl rather than fixed intermittent bolus doses. Hence we could arrive at the exact fentanyl requirements. We observed that the VAS at baseline was just comparable to the placebo group indicating no added advantage with pregabalin premedication. However this is in contrast to the observation made by Jokela *et al.* [11] where 150 mg pregabalin reduced the VAS score significantly. This can be explained by the multimodal analgesia technique employed by them with addition of Ibuprofen 800 mg in their study protocol.

In a study on postoperative pain control following hip arthroplasty, Mathierson *et al.* [12] had found that 300 mg pregabalin reduced post-operative morphine requirement by 50% but they observed greater incidence of sedation, nausea and vomiting. However in the present study we observed pregabalin had opioid sparing effect without any adverse effects.

Pregabalin is found to be drug with good safety profile. It is not protein bound and not metabolized and hence the drug has no major interactions with the blood levels of other drugs. Pregabalin acts on the N type calcium channels. The cardiac and peripheral tissues have the L type calcium channels. The lack of action on the cardiac type calcium channels explains the drug's relative cardiac safety. The common side effects with pregabalin are the drowsiness and somnolence.

The novel action on $\alpha_2\delta$ subunit of neuronal calcium channels resulting in the blunting of the release of excitatory neuro aminoacids makes pregabalin a unique choice in many clinical scenarios including suppression of pressor response to laryngoscopy and intubation.

The present study did not include the evaluation of the anxiety level, measurement of serum catecholamine level and intraoperative requirement of fentanyl. These could have provided added information.

Summary and Conclusion

This prospective, randomized, double blinded and placebo controlled study evaluated the efficacy of single oral dose of 150 mg pregabalin given an hour before induction on attenuation of haemodynamic response to laryngoscopy and intubation.

Pregabalin 150 mg causes significant attenuation of haemodynamic response to laryngoscopy tracheal intubation and reduces post-operative fentanyl requirement without any major side effects in patients undergoing abdominal surgery.

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