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A Comparative Study of the Effects of Premedication with Oral Clonidine versus Oral Pregabalin in Patients Undergoing Lumbar Spine Surgery

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Abstract

Aim: The aim of this study was primarily to compare the efficacy of single pre operative dose of oral pregabalin versus oral clonidine in attenuation of pressor response to direct laryngoscopy and intubation and on the intra operative haemodynamic stability in patients undergoing elective lumbar spine surgery. The secondary outcome was to evaluate the intra operative opioid consumption in both the drug groups. *Background:* Direct laryngoscopy and intubation are painful stimuli which cause reflex sympathetic nervous system stimulation resulting in untoward haemodynamic response. This study compares the effect of single oral pre-operative dose of clonidine versus oral pregabalin in attenuation of the pressor response to direct laryngoscopy and intubation and the intra-operative haemodynamics in patients undergoing lumbar spine surgery. *Materials & Methods*: This randomized double blinded trial was conducted in our tertiary care hospital. After obtaining informed written consent, sixty adult patients belonging to ASA I and ASA II undergoing elective lumbar spine surgery under general anaesthesia were randomly divided into two groups of thirty each. Group C received 100 μg of oral clonidine and Group P received 150 mg of oral pregabalin ninety minutes prior to induction of anaesthesia. Systolic blood pressure (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and heart rate (HR) were measured at three time points; baseline(3 min before induction),just before laryngoscopy, 1, 3, 5, 10 and 15 min after intubation.The intra operative haemodynamics and fentanyl consumption was recorded for all patients. Statistical analysis was done using students' t test and chi square test. *Results:* Both drugs attenuated the haemodynamic pressor response associated with laryngoscopy and endotracheal intubation. The reduction in SBP, DBP, and MAP was comparable in both groups but the tachycardia was attenuated significantly in the clonidine group (P value< 0.05). The intra operative fentanyl consumption was lesser in the clonidine group than the pregabalin group (P value=0.0069). *Conclusions:* Oral pregabalin and clonidine successfully attenuated the pressor response to direct laryngoscopy and intubation. No adverse effects were observed with the doses used in our study. The intraoperative analgesic consumption was less in both the groups.

Keywords: Clonidine; Lumbar Spine Surgery; Pregabalin; Premedication; Pressor Response.

Introduction

Laryngoscopy and tracheal intubation are noxious stimuli that evoke a transient but marked sympathetic response manifesting as increase in heart rate, blood pressure and arrhythmias. Various drugs have been used as preoperative medication to attenuate the stress response to laryngoscopy and intubation. Clonidine is primarily a α2 agonist used primarily for its antihypertensive effects (α2 to α1 receptor ratio of 200:1). Alpha-2 receptors are adrenoreceptors that are located primarily on presynaptic nerve terminals. Activation of these receptors inhibits adenylate cyclase activity, which in turn decreases the entry of calcium into the neuronal terminal, which limits norepinephrine release. This leads to an overall decrease in sympathetic outflow, causing peripheral vasodilatation, as well as negative chronotropic effects causing a reduction in blood pressure. This decrease in central sympathetic outflow does not

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affect baroreceptor reflexes, therefore not causing orthostatic hypotension. Stimulation of these receptors in the central nervous system has also been shown to have sedative properties. Clonidine provides sedation and anxiolysis, decreases analgesic dosage requirements, decreases MAC (minimum alveolar anaesthetic concentration), reduces catecholamine levels and lowers heart rate and blood pressure during anaesthesia and reduces postoperative oxygen consumption [1,2,3]. Gabapentinoids (gabapentin and pregabalin) 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 of gammaamino butyric acid (GABA) [4,5]. Pregabalin has anxiolytic, sedative, antiallodynic, antihyperalgesic, antinociceptive and antisecretory properties [4,5]. It acts by presynaptic binding to the $\alpha 2\gamma$ subunit of voltagegated calcium channels that are widely distributed in the spinal cord and brain [4,5,6]. By altering calcium currents, pregabalin reduces or modulates the release of several excitatory neurotransmitters, including glutamate, nor epinephrine, substance P, and calcitonin generelated peptide, producing inhibitory modulation of overexcited neurons and returning them to a normal state [7]. Pregabalin is effective in neuropathic pain, post herpetic neuralgia, reflex sympathetic dystrophy, acute postoperative pain, diabetic neuropathy and reduces the intra operative and post-operative opioid requirements [7,8]. Pregabalin has been used for attenuation of pressor response in normotensive patients [9-12]. Pregabalin has a linear pharmacokinetic profile with a time to peak plasma concentration up to one hour, and oral bioavailability of 90%. It is only slightly metabolized by liver, and up to 98% of administered dose is eliminated unchanged by kidneys [8]. Eren et al evaluated the effectiveness of pregabalin in suppressing the hemodynamic response to intubation in lumbar spinal surgeries [13]. Taghipour etal evaluated the efect of oral clonidine premedication in reducing blood loss during lumbar spine surgeries [14]. No randomised controlled study has been carried out to compare oral clonidine versus oral pregabalin to attenuate the pressor response of airway instrumentation in patients undergoing elective spine surgeries under general anaesthesia. Controlled, or deliberate, hypotension has been used for many years as a means of reducing intraoperative blood loss and facilitating surgical exposure, reducing the duration of surgery and the need for blood transfusion. As an oral premedication, clonidine can reduce surgical blood loss in lumbar spine posterior fusion surgery, even at the same levels of mean arterial pressure (MAP) with the control group and its use can be studied in more complicated spine surgeries, such as scoliosis and spinal deformity surgeries.[14]

Material and Methods

After obtaining ethical committee approval and informed written consent, this prospective, randomised, double blind, controlled study was conducted on sixty patients undergoing elective lumbar spine surgeries under general anaesthesia at our tertiary care hospital over a period of nine months. The inclusion criteria were patients belonging to ASA I and II, aged between 20 to 65 years, with a BMI of 18-25, belonging to either sex who were posted for elective lumbar spine surgery under general anaesthesia. The exclusion criteria were patients with allergy to clonidine or pregabalin, cerebrovascular, neurologic, respiratory and Ischemic heart disease, renal and hepatic disease, head injuries, diabetes mellitus, BMI >25, patients on beta blockers, anti- hypertensives, anti-depressants, anti-anxiety drugs, anticonvulsants or anti-psychotics and those with anticipated difficult airway. The patients enrolled in the study were randomly divided into two groups using computer based randomization. Baseline heart rates (HR), blood pressure (BP), mean arterial pressure (MAP) were recorded before giving the study drug ninety minutes before surgery. Pre hoc power calculation suggested that a minimum of 25 patients per group would detect a 15% difference in haemodynamic response to laryngoscopy and endotracheal intubation and peri operative 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. A total of 63 patients were enrolled in the study but one patient in group C and two patients in group P had an intubation time of more than 120 seconds and were dropped from the study (Figure 1).

Group C (n=30) – Patients in this group received 100µg of oral clonidine 90 minutes before induction of anaesthesia.

Group P (n=30) – Patients in this group received 150mg of oral pregabalin 90 minutes before induction of anaesthesia.

Study drugs containing clonidine and pregabalin were administered in a double blinded way by an anaesthesiologist not involved in the data recording. An expert anaesthesiologist in the operating room

performed laryngoscopy and endotracheal intubation and a blinded observer collected the data.

In the operating room, after establishing an intravenous line, ringer's solution was started as maintenance intra operatively. Non invasive blood pressure, electrocardiography, pulse oximetry and capnography and core temperature were monitored. The baseline heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial blood pressure (MAP) were recorded. Patients were premedicated with intravenous fentanyl 2µg/kg and midazolam 1mg. After pre oxygenation, anaesthesia was induced with IV thiopentone sodium 5 mg/kg and after loss of eyelash reflex, IV vecuronium 0.1mg/kg was given and patient's lungs were manually ventilated with 100% oxygen for three minutes. After that direct laryngoscopy was performed by using a Macintosh laryngoscope blade of appropriate size and tracheal intubation was accomplished within 15 seconds by the expert anaesthesiologist in the operating room using a suitable sized cuffed oral endotracheal tube.

After confirming bilaterally equal air entry and capnographic trace the endotracheal tube was fixed and anaesthesia was maintained with a mixture of 50:50 oxygen and nitrous oxide and isoflurane 1% with intermittent doses of 0.02mg/kg of vecuronium. The patient's lungs were mechanically ventilated with tidal volume of 8ml/kg and a respiratory rate of 12/ min to maintain end tidal CO_2 of 35 mmhg. The HR and BP (SBP, DBP and MAP) were measured at three time points: baseline (3 min before induction), just before laryngoscopy and post intubation (at 1, 3, 5, 10, 15 min after starting laryngoscopy). Towards the end of the procedure, residual neuromuscular block was reversed with 50µg/kg of neostigmine and 10 µg/kg glycopyrrolate. After extubation the patients were shifted to the post anaesthesia care unit for further monitoring.

Statistics

Statistical analysis was performed using SPSS version 16.0 (SPSS). Student's 't'-test was used to analyse the differences in the parameters between the two groups. A P value less than 0.05 was considered statistically significant.

The Following Parameters were Studied

1. Heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure were recorded at three time points- three minutes before induction, just before laryngoscopy, and post intubation (at 1,3,5,10 and 15 minutes after laryngoscopy) and the intraoperative average values.
2. Occurrence of adverse effects like hypotension, hypertension, arrhythmias, tachycardia, bradycardia, PONV (post-operative nausea vomiting), nystagmus and dryness of mouth were recorded for each case.
3. Total intraoperative dose of fentanyl in micrograms.
4. The Ramsay Sedation Scale was assessed before induction of anaesthesia and at recovery, six hours after extubation. 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 cooperative 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).

Results

The demographic parameters such as age, sex and BMI (body mass index) were comparable in both groups. (Table 1). However there was more number of males in both groups. The baseline heart rate was 70.1±8.3 in group C and 77.6±8.3 in group P (P value< 0.05). Similarly the heart rate measured just before laryngoscopy and one minute after intubation was lower in group C compared to group P (P value< 0.05) as shown in Table 2. The heart rate measured at three minutes duration after intubation was comparable in both groups.

There afterwards the mean heart rate measured at five minutes, ten minutes and fifteen minutes after intubation was significantly low in group C compared to group P (P value<0.05). The average intra operative heart rate was significantly lower in group C compared to group P(P value=0.0001). The mean MAP at baseline, before laryngoscopy, at 1, 3, 5, 10 and 15 minutes following intubation and the average intra operative MAP was comparable in both the groups (P value>0.05). The systolic and diastolic pressures measured at these intervals were

also comparable in both groups (P value>0.05) [Table 3].

There was however a significant differences in the intra operative consumption of fentanyl between the two groups during surgery [Table 5]. The average intra operative fentanyl consumption was 105.8±16.3 mcg in group C and 119.16±20.43 mcg in group P. (P value=0.0069) Ramsay sedation scores measured before induction (baseline) and six hours after extubation were also similar between the groups [Table 4]. No major untoward effects like tachycardia, bradycardia, arrhythmias, and hypotension were seen due to the study drugs in both groups. In group P, three patients had dizziness which subsided in two hours, one patient had drowsiness and one patient had post-operative nausea and vomiting. In group C, two patients complained of dry mouth, two patients had drowsiness and one patient had post-operative nausea and vomiting [Table 6].

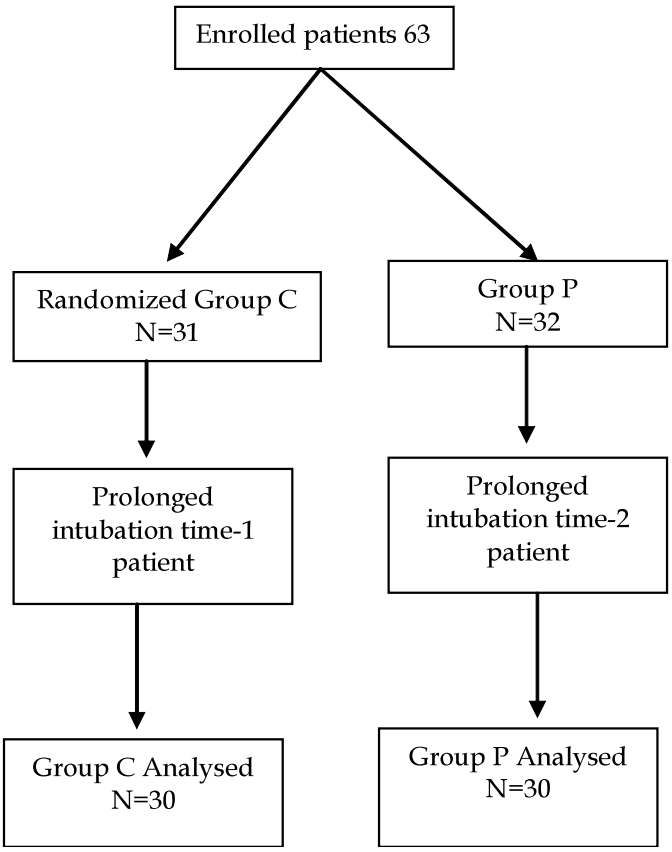

Fig. 1: Consort diagram showing flow of participants

Table 1: Demographic parameters

	Group C (n=30)	Group P (n=30)	P value
Age in years (mean ±SD)	38.8±8.71	41.4±9.92	0.285
Gender (male: female)	21:9	19:11	0.947
BMI (mean ±SD)	23.79±2.33	24.38±2.09	0.306

SD (Standard deviation), BMI(body mass index)

Table 2: Heart rate variation in the two groups

Heart rate changes	Group C	Group P	P value
Baseline HR (mean ± SD)	70.1±8.3	77.6±8.3	0.0001
Just before laryngoscopy (mean ± SD)	70.2±8.6	76.9±8.6	0.0038
1 minute after intubation (mean ± SD)	80.2±6.8	88.7±6.8	0.0001
3 minutes after intubation (mean ± SD)	83.3±10.2	85.3±6.3	0.3646
5 minutes after intubation (mean ± SD)	77.2±8.9	81.5±7.3	0.0453
10 minutes after intubation (mean ± SD)	70.2±8.82	78.0±6.9	0.0003
15 minute after intubation (mean ± SD)	66.6± 8.6	74.8±8.1	0.0003
Average intra operative HR	65.6±8.8	78.6±8	0.0001

HR (heart rate)

Table 3: Systolic blood pressure, diastolic blood pressure and mean arterial pressure variation in the two groups (in mmhg)

Variable	Group	Baseline (mean±SD)	Just before laryngoscopy (mean±SD)	1 min after intubation (mean±SD)	3 min after intubation (mean±SD)	5 min after intubation (mean±SD)	10 min after intubation (mean±SD)	15 min after intubation (mean±SD)	Mean intra operative value
SBP	Group C	132.4±4.7	121.6±16.8	138.1±18.7	124.6±22.1	119.3±22.0	115.2±21.8	112.4±21.5	118±21
	Group P	130.1±8.1	118.8±13.7	132±15.9	121.4±19.9	117.6±21.4	114.2±21.4	111.7±20.8	122±23
	P value	0.1838	0.341	0.1787	0.5579	0.7627	0.8616	0.8985	0.4846
DBP	Group C	80.7±21.1	76.2±20.4	84.9±20	80.8±19.7	79.3±19.4	77.8±19.2	76.16±18.9	72±13
	Group P	82.4±20.1	75.7±20.8	85.3±21	78.7±21.4	76±21	75.3±20.8	73.5±20.8	76±21
	P value	0.7505	0.9254	0.9400	0.6940	0.5297	0.6304	0.6061	0.3787
MAP	Group C	98±18.7	91.3±18.4	103±18	95±17.6	93±17.2	90±16.9	88±16.5	89±16.2
	Group P	98.5±20.9	90.3±20.4	100.9±19.9	92.9±19.5	89.9±19.1	88±18.8	86.2±18.4	90±18.4
	P value	0.9225	0.8427	0.6698	0.6631	0.5163	0.6664	0.6934	0.8240

SD (Standard deviation), SBP (Systolic blood pressure), DBP (diastolic blood pressure) and MAP (mean arterial pressure)

Table 4: Ramsay sedation scale

Average Ramsay score	Group C (n=30)	Group P (n=30)	P value
Before induction	2.7±0.54	2.5±0.5	0.1420
Six hours after extubation	2.16±0.37	2.16±0.38	1.0000

Table 5: Intra operative fentanyl consumption

	Group C	Group P	P Value
Average intra operative fentanyl (mcg)	105.8 ± 16.3	119.16 ± 20.43	0.0069

Table 6: Adverse events in the groups

Adverse events	Group C (Clonidine)	Group P (Pregabalin)
Bradycardia	0	0
Tachycardia	0	0
Arrhythmia's	0	0
Hypertension	0	0
Hypotension	0	0
PONV	1	1
Dizziness	0	3(subsided after 2 hrs)
Peripheral edema	0	0
Nystagmus	0	0
Dry mouth	2	0
Drowsiness	2	1

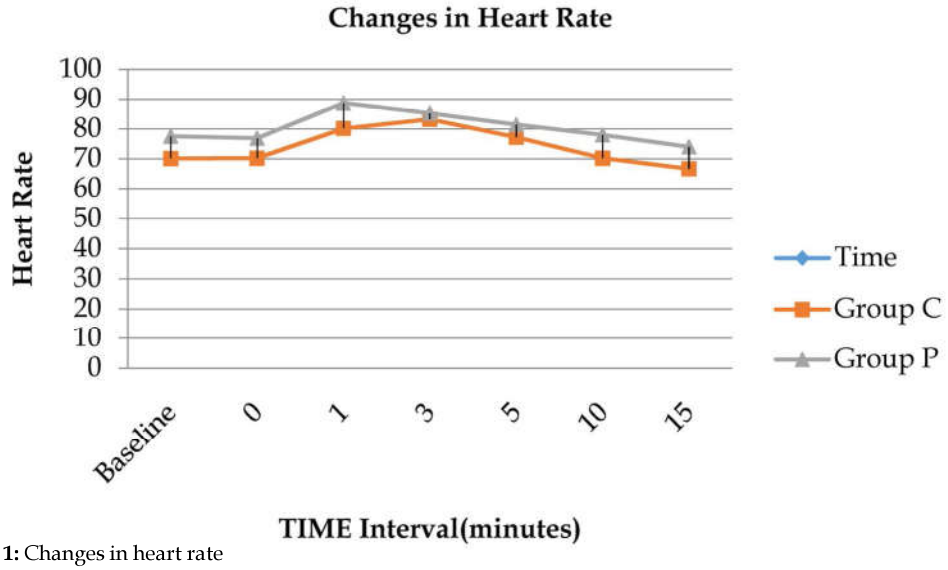

Fig. 1: Changes in heart rate

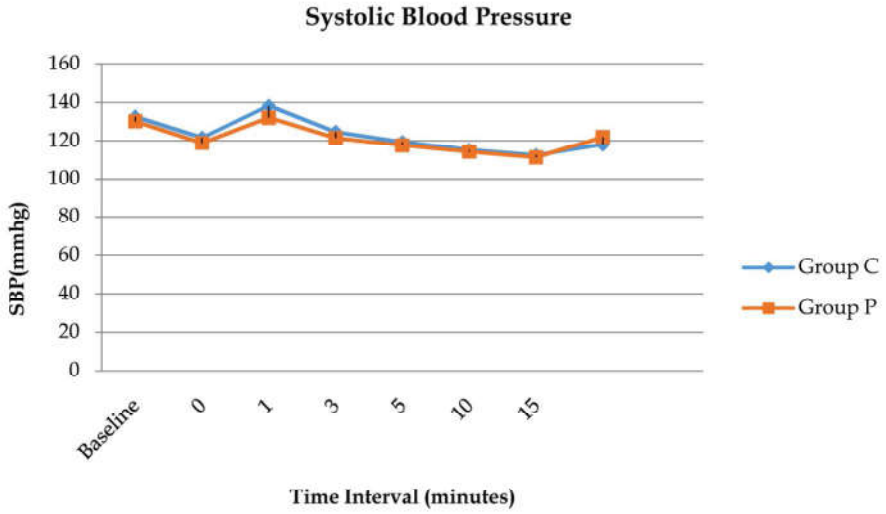

Fig. 2: Changes in systolic blood pressure

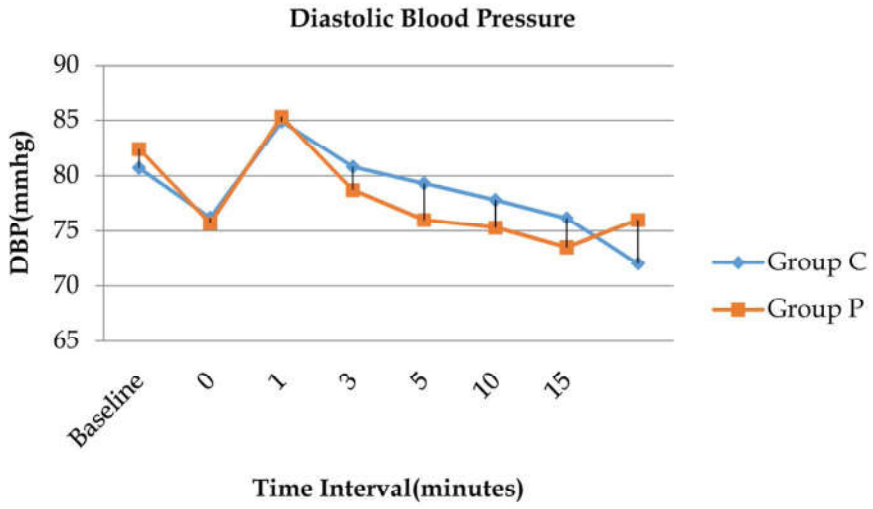

Fig. 3: Changes in diastolic blood pressure

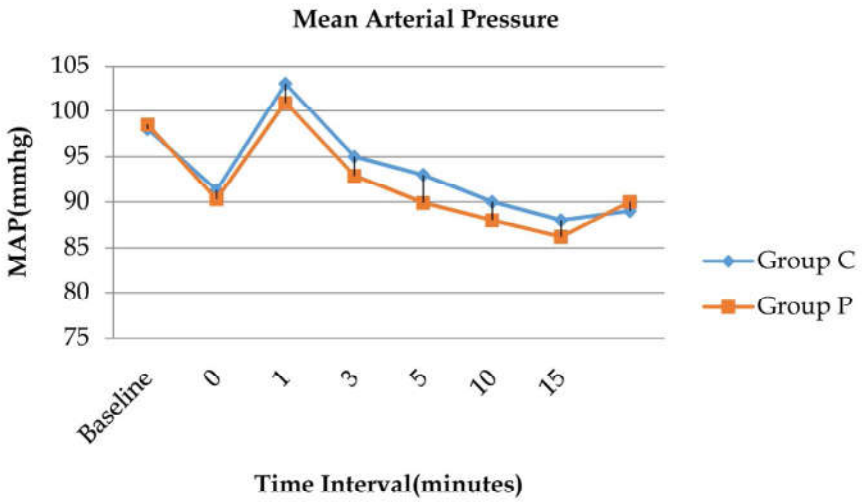

Fig. 4: Changes in mean arterial blood pressure

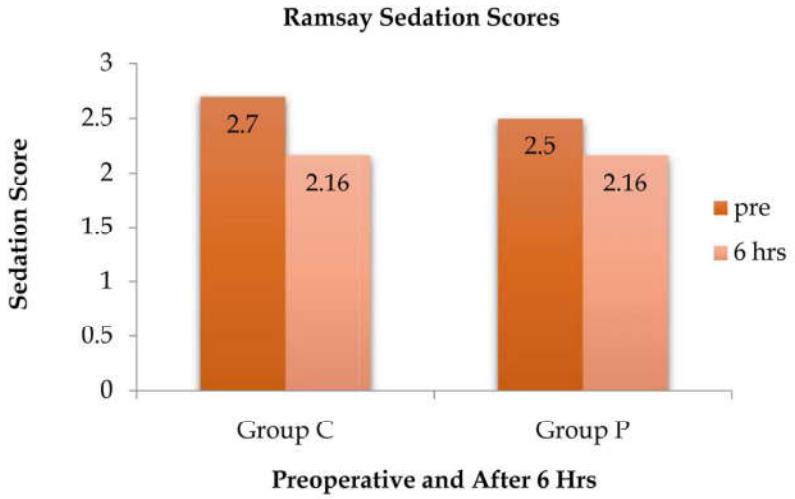

Fig. 5: Ramsay sedation scores

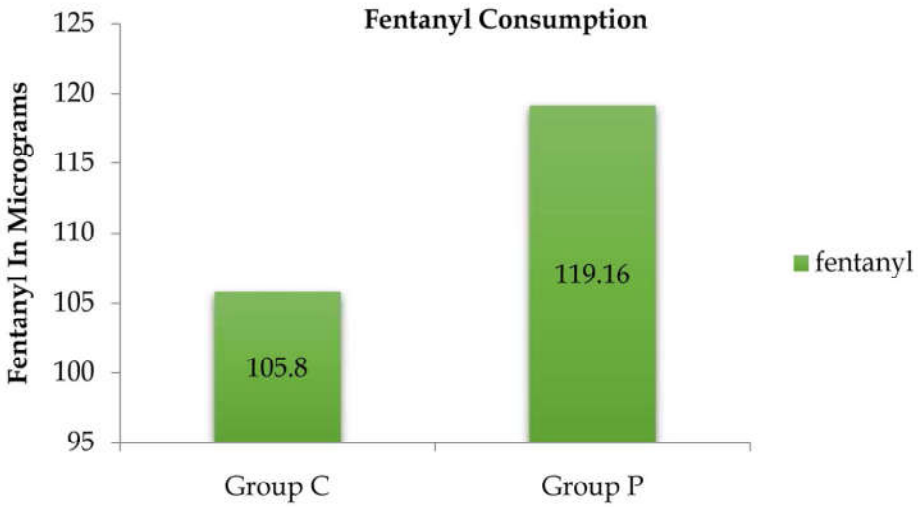

Fig. 6: Intra operative fentanyl consumption

Discussion

Pregabalin is recently used as an adjuvant for high quality acute postoperative pain control. A multimodal approach has been suggested to improve postoperative analgesia and to reduce opioid related side effects [20]. Mathiesen et al. demonstrated that single preoperative dose of pregabalin 300 mg resulted in approximately 50% reduction in 24 hour morphine requirements in patients undergoing hip surgery [21].

In another study, perioperative pregabalin is associated with better pain relief and functional outcomes three months after lumbar disc surgery [22]. Therefore, its pharmacologic, analgesic and anxiolytic properties make it a useful drug for premedication [19]. The effect of pregabalin on the haemodynamic response to laryngoscopy and tracheal intubation might be explained by its inhibitory effects on membrane voltage gated calcium channels.

White et al indicated that preoperative medication with pregabalin at doses 75 to 300 mg was not effective in attenuating acute preoperative anxiety, on the other hand pregabalin at the dose of 300 mg produced increased level of sedation before and after ambulatory surgery [11].

In this study, the dose of pregabalin which was chosen as 150 mg did not produce sedation or drowsiness. The efficacy of pregabalin in our study to suppress intubation response correlates well with the report of Eren et al [13]. The intra operative opioid consumption was less in both the groups though lesser in group C than group P. This is contrary to the study results by Jokela etal who 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 [20].

In our study we did not observe any adverse effects or significant opioid sparing effect with pregabalin because of the lower doses used. The stable hemodynamic variables in group P in the present study were an indication of adequate analgesia and sedation with oral pregabalin. This correlates with studies done by Salman et al [12] and Sundar et al [9]. Hence both the drugs produced comparable attenuation of pressor response to laryngoscopy and intubation which correlates with the study of Gupta et al [10]. In our study oral premedication with pregabalin 150 mg one hour before surgery attenuated the haemodynamic response to laryngoscopy and endotracheal intubation.

Controlled hypotension in the peri operative period is the common strategy used to reduce blood loss in lumbar spine surgery in prone position. Apart from this, the haemodynamic stress response to laryngoscopy and endotracheal intubation are noxious stimuli which can be detrimental to patients with cardiovascular disease. Even short episodes of cardiovascular stimulation can have detrimental effects on the coronary circulation leading to high morbidity and mortality [17,18].

Clonidine is an alpha-2 adrenoceptor agonist that effects sedation and anti-nociception by stimulating central alpha-2 adrenoceptors at different sites in the central nervous system. Stimulation of medullary alpha-2 adrenoceptors decreases sympathetic tone and increases vagal activity, which blunts the hemodynamic responses to stressful stimuli. In addition, stimulation of presynaptic alpha-2 adrenoceptors decreases the release of norepinephrine at peripheral sympathetic nerve endings, which decreases sympathetic tone. Even a low dose of clonidine can attenuate the preoperative stress response and thus is recommended in cardiovascular high risk patients and small doses, like 75–150 μg attenuate the stress response before coronary artery bypass graft surgery [16].

In our study we have compared a single low dose oral clonidine versus oral pregabalin in attenuatiing the pressor response to laryngoscopy and intubation. There is good evidence from the literature that clonidine is a powerful drug that attenuates stress response of various causes [10,15-18].

Conclusion

Premedication with 150 mg of oral pregabalin or 100ìg of oral clonidine attenuated the haemodynamic pressor response associated with laryngoscopy and endotracheal intubation in patients undergoing lumbar spine surgery under general anaesthesia. There was a significant reduction in SBP, DBP, and MAP which was comparable in both groups but the tachycardia was attenuated better in the clonidine group. The Ramsay sedation scores measured pre operatively and six hours after extubation were comparable in both groups with the doses used. The intra operative fentanyl consumption was lesser in the clonidine group than pregabalin group.

Conflict of Interest

None

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