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A Comparative Study of Oral Pregabalin and Clonidine as Premedication in Patients Undergoing Laparoscopic Cholecystectomy

Lalnundiki[1], Chawngthu Vanlalhlua[2]
[1]*Assistant Professor, Department of Anaesthesiology, Zoram Medical College, Mizoram.*
[2]*Associate Professor, Department of General Surgery, Zoram Medical College, Mizoram.*
Corresponding Author: Dr Chawngthu Vanlalhlua, M.S, FAIS, FMAS, EFIAGES, FIAGES.

Introduction: *The purpose of this study was to evaluate the efficacy of oral Pregabalin and oral Clonidine premedication with regards to attenuation of haemodynamic response to laryngoscopy and intubation, postoperative pain, analgesic requirement following surgery and incidence of postoperative nausea and vomiting (PONV).*
Materials and Methods: *The study comprised of 100 patients divided into two groups of 50 each, in the department of Anaesthesiology/Surgery, Zoram Medical College, Falkawn, Mizoram, during the period of two years from March 2018 to February 2020. Patients of ASA grade I and II, aged between 18 and 60 years of both sexes scheduled to undergo Laparoscopic Cholecystectomy under general anaesthesia were included. Patients with difficult airway, BMI more than 25, known hypersensitivity to Pregabalin and Clonidine were excluded.*
Results: *The result shows that Clonidine has better result in haemodynamic response to laryngoscopy and intubation, better control of postoperative pain and lesser analgesic requirement following surgery than Pregabalin but no statistically significant difference in the incidence and severity of PONV. Conclusion: Clonidine is superior to Pregabalin for attenuation of haemodynamic response to laryngoscopy and endotracheal intubation, and it significantly reduces the requirement of analgesic in postoperative period.*
Keywords: *Clonidine, Pregabalin, Haemodynamic response, postoperative pain, postoperative nausea and vomiting.*

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I. Introduction

Intubation is the gold standard in elective surgeries under general anaesthesia. Laryngoscopy and intubation is associated with undesirable haemodynamic variability. Various drugs like beta blockers, lignocaine etc have been used over the last few decades to attenuate this haemodynamic stress response. Perioperative care requires adequate pain relief and control of postoperative nausea and vomiting (PONV). Opioids have remained the mainstay of treatment for postoperative pain; however its side effects of respiratory depression, nausea, vomiting, purities and delayed recovery of bladder and bowel function are undesireable[1]. Postoperative nausea and vomiting have been treated by a wide spectrum of drugs. However, there is paucity of drugs that are useful in achieving all the above goals.

In recent times, few drugs when used as premedicant have been found to be useful in achieving all the above goals. These include alpha2 adrenoreceptor agonist (Clonidine) and gabapentinoids (Gabapentin and Pregabalin). Clonidine is an alpha2 adrenoreceptor agonist with sedative and analgesic effects; it has also shown to have beneficial effects of blunting haemodynamic responses to laryngoscopy and tracheal intubation[2].

Gabapentin is an anticonvulsant that has antinociceptive and antihyperalgesic properties. In pain models, it has shown antihyperalgesic properties[3]. It has been studied that gabapentinoids can block central sensitization by decreasing the influx of calcium ions. In addition, Gabapentin as a premedication was effective in reducing PONV and postoperative analgesic requirement.

Pregabalin is a newer gabapentinoid which has also been alleged to possess anxiolytic, analgesic and antiepileptic activity[4]. Pregabalin is currently in use for treatment of neuropathic pain, fibromyalgia etc[5]. There is increasing interest regarding the evaluation of Pregabalin in the management of acute post-surgical pain and reduction of postoperative nausea and vomiting. It is being evaluated as a premedicant to help in attenuating the haemodynamic response to laryngoscopy and intubation. Pregabalin has a more favourable pharmacokinetic profile than that of Gabapentin with lesser side effects.

II. Materials And Methods

This prospective, randomized, observational study was conducted in the department of Anaesthesiology and Surgery, Zoram Medical College Hospital, Falkawn, Mizoram, India, during the period of two years starting from April 2018 to March 2020. Informed consent was taken from each patient. After obtaining approval from the institutional board, hundred patients of ASA grade I and II, aged 18-60 years of both gender undergoing elective Laparoscopic Cholecystectomy under general anaesthesia were included for the study. Exclusion criteria are patients with difficult airway, BMI > 25, known hypersensitivity to Pregabalin and Clonidine, long standing medical (hepatic or renal) or psychiatric illness, history of chronic pain, patients on hypnotics or sedatives, on anticoagulant therapy, and with suspected hiatus hernia or GERD.

100 patients were allocated randomly by computer generated random number table to Group P (oral Pregabalin) and Group C (oral Clonidine). The observer was blinded to the drug being administered to the patient.

A detailed preanaesthetic evaluation including all routine investigations was carried out in all patients. Age, sex, body mass index, educational status of all patients recorded. All patients were kept nil per mouth overnight. Patients were also explained and familiarized with visual analogue scoring system. Group P and C patients were administered Capsule Pregabalin 150mg and Tablet Clonidine orally with a sip of water 1 hour before surgery respectively.

All patients were shifted to the operation room and all monitor attached. Baseline vital parameters were recorded after stabilizing the patient for 5 minutes. An intravenous line was established and standard anaesthetic protocol was followed. All patients were premedicated with iv Inj Ranitidine 50mg. Patients were induced with Inj Propofol 2mg/kg, Sevoflurane (2-3%) and 66% Nitrous Oxide in Oxygen and neuromuscular blockage was achieved with Inj Vecuronium 0.1mg/kg. bag and mask ventilation was done for 3 minutes followed by laryngoscopy and intubation using orotracheal cuffed tube of appropriate size. Inj Fentanyl 2microg/kg was given intravenously 10 minutes after intubation. Anaesthesia was maintained with Sevoflurane and Nitrous oxide in Oxygen and Inj Vecuronium

Blood pressure and heart rate were measure and recorded before induction, before laryngoscopy, at laryngoscopy and intubation which was taken as 0 minute and then every minute for the first 10 minutes after induction. Subsequently every 10 minute, vitals were observed till the completion of surgery.

In the postoperative ward, VAS on a scale of O to 10 was recorded both at rest and coughing and subsequently at 1, 2, 3, 4, 8, and 24 hours after surgery. At each time the VAS was recorded at rest (static) and after coughing (dynamic). The rescue analgesic was administered when the patient had a VAS more than 3. The rescue analgesic was i.m Inj Diclofenac 1mg/kg. Total analgesic requirement in 24 hrs was recorded.

The severity of postoperative nausea and vomiting was graded on a three point scale (0, 1-nausea, 2-vomiting. The rescue antiemetic was i.v Inj Ondansetron 0.1mg/kg. Total antiemetic given in 24hrs was recorded. All patients with laryngoscopy and intubation exceeding 30 seconds of the surgical procedure extending beyond 90 minutes were excluded from the statistical analysis.

Statistical analysis: $P < 0.05$ was considered to be significant. Sample size was 100 (50 each group) giving the power of the study to be 80%, Qualitative data were analyzed using Chi Square test of Fischer Exact test. Quantitative data were analyzed using Unpaired 't' test and non-parametric Wilcoxan Mann Whitney test. All data was statistically analyzed using Statistical Package for the Social Sciences statistical software.

III. Results And Observations

The age of patients ranged from 18 to 60 years in this study. The maximum incidence (44%) was found in the age group of 18-30 years in Group P whereas 34% were in the age group of 31-40 yrs in group C. The mean age in Group P and C was 35.38yrs and 37.68yrs respectively.

Table 1: Percentage of each Age group.

Age Group	Pregabalin	Clonidine
18-30 yrs	44%	30%
31-40 yrs	28%	34%
41-50 yrs	14%	26%
51-60 yrs	14%	10%

Chart I: Percentage of each Age group.

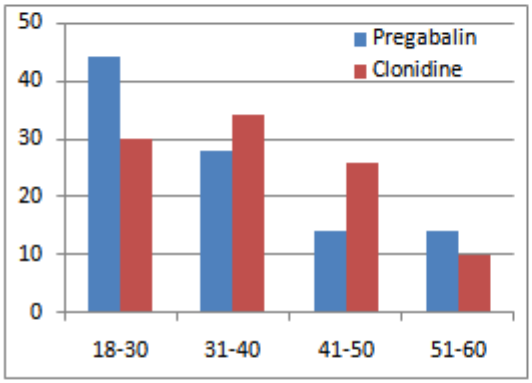
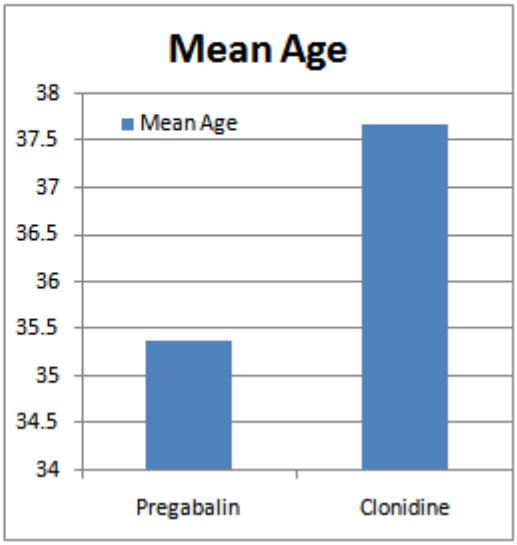


Chart II: The mean Age of each group

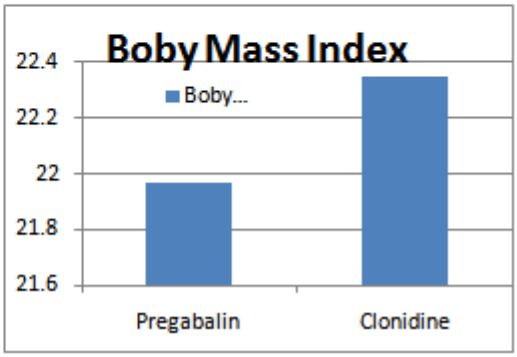


The Mean Body Mass Index in Group P was 21.97 and that of Group C was 22.35.

Table 2: The Mean Body Mass Index

Group	BMI
Pregabalin	21.97
Clonidine	22.35

Chart III showing mean BMI



The percentage of ASA grade in each group is shown in Table 3.

Table 3: Percentage of ASA grade

Group	ASA 1	ASA 2
Pregabalin	**86%**	**14%**
Clonidine	**78%**	**22%**

Chart IV: shows percentage of ASA1 and ASA2 in each group

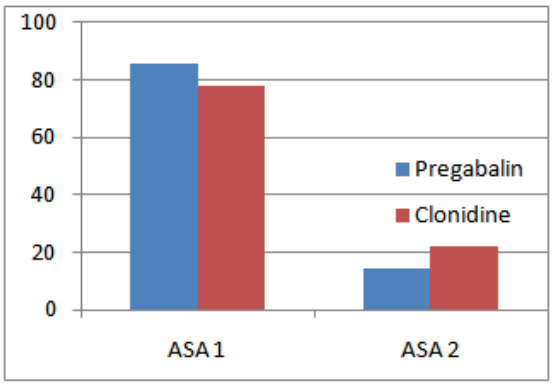


Table 4 shows that the changes in heart rate before induction, before laryngoscopy, at laryngoscopy and 1-10 minutes following laryngoscopy and intubation. Heart rate is significantly lower in group C at laryngoscopy and thereafter for the first 10 minutes analyzed by Unpaired't' test (p-value < 0.05).

Table 4: Changes in heart rate

Group	Before Induction	Before Laryngoscopy	At Laryngoscopy	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min
P	87	84	103	100	96	95	93	91	89	88	85	83	82
C	86	81	96	93	89	86	83	82	79	76	75	74	72
p-value	0.887	0.198	0.014	0.025	.009	0.007	0.001	0.003	0.000	0.000	0.00	0.001	0.000

Chart V: showing changes in heart rate.

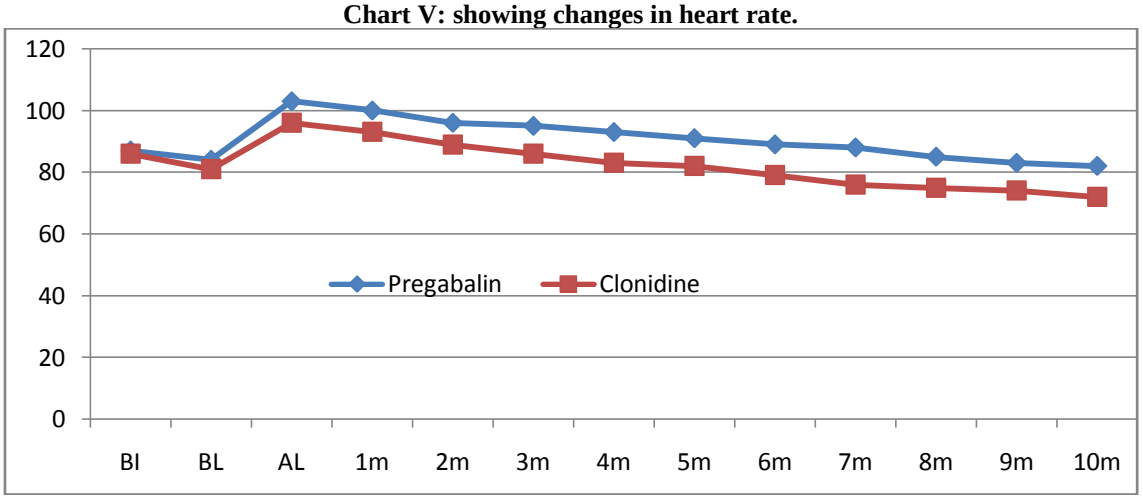


Table 5 shows that the changes in mean blood pressure before laryngoscopy, at laryngoscopy and 1-10 minutes following laryngoscopy and intubation. Mean blood pressure is significantly lower in group C at 5, 7, 9, and 10minutes following intubation as analyzed by Unpaired 't' test (p-value < 0.05).

Table 5: Changes in Mean BP

Group	Before Laryngoscopy	At Laryngoscopy	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min
P	77	106	99	93	89	88	86	83	82	81	79	78
C	75	102	98	92	89	85	81	79	76	75	73	72
p-value	0.398	0.062	0.798	0.614	0.945	0.312	0.042	0.055	0.014	0.010	0.005	0.003

Line chart VI showing changes in Mean BP

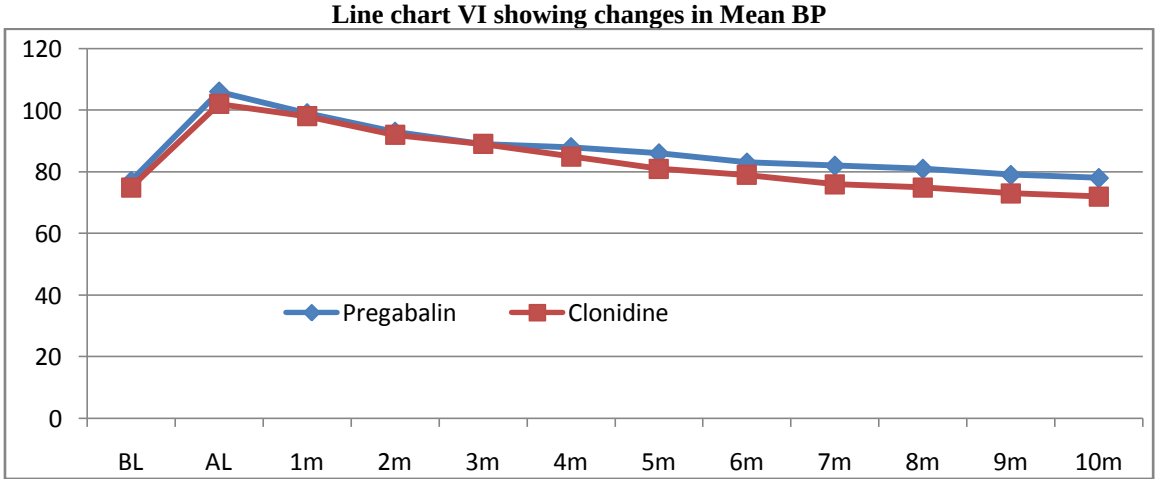


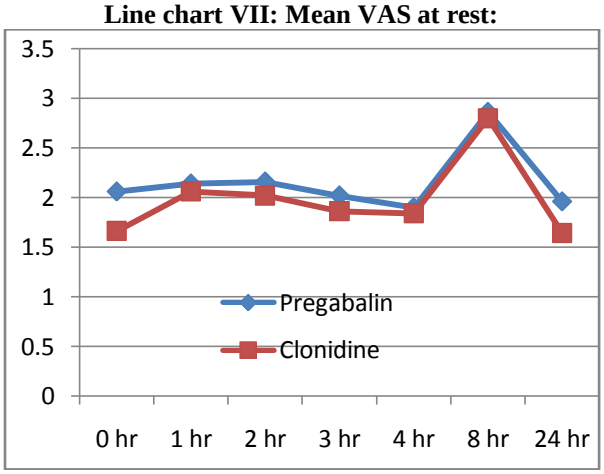
Table 6 shows the mean visual analogue score at rest at 0 hr, 1 hr, 2 hr, 3 hr, 4 hr, 8 hr and 24 hours post surgery. The VAS Score is significantly less in group C at 24 hours post surgery as analyzed by Mann Whitney Test

Table 6: Mean VAS at rest and on coughing

Group	VAS AT REST (MEAN)						
	0 hr	**1 hr**	**2 hr**	**3 hr**	**4 hr**	**8 hr**	**24 hr**
Pregabalin	2.06	2.14	2.16	2.02	1.90	2.86	1.96
Clonidine	1.66	2.06	2.02	1.86	1.84	2.80	1.64
p-value	0.235	0.508	0.423	0.412	0,631	0.740	0.014

Group	VAS AT ON COUGHING (MEAN)						
	0 hr	**1 hr**	**2 hr**	**3 hr**	**4 hr**	**8 hr**	**24 hr**
Pregabalin	2..78	2.88	2.92	2.76	2.60	3.62	2.54
Clonidine	2.24	2.80	2.78	2.50	2.62	3.54	2.22
p-value	0.145	0.677	0.471	0.211	0,822	0.849	0.086

Line chart VII: Mean VAS at rest:



Line chart VIII: Mean VAS on coughing:

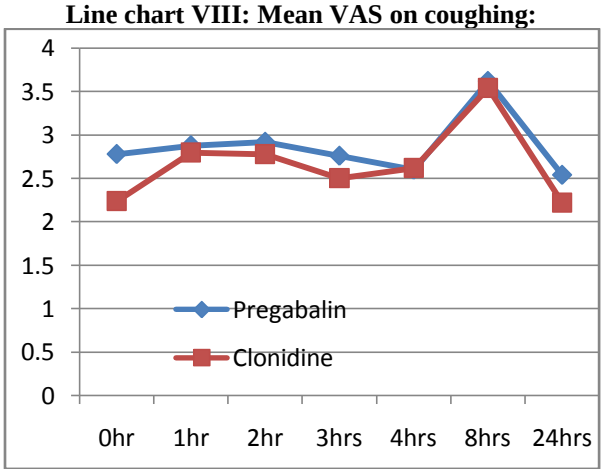


Table 7 shows the total number of times analgesic given in 24 hours. The total analgesic requirement is significantly less in Clonidine group as analyzed by Mann Whitney Test (p-value = 0.048)

Table 7: Total no of times analgesic given in 24 hours

Groups	Total no of times **analgesic** given in 24 hours
Pregabalin	2.50
Clonidine	2.22
p-value	0.048

Table 8 shows the incidence and severity of postoperative nausea and vomiting between the two groups. The postoperative nausea and vomiting was graded on a three point scale (0-no nausea and vomiting, 1-nausea, 2-vomiting). There is no significant difference in the incidence and severity of PONV as analyzed by Chi-Square test.

Table 8: Incidence and severity of PONV

Groups (n=50)		Severity of PONV		
		0	**1**	**2**
Pregabalin	**Count**	24	13	13
	%	48%	26%	26%
Clonidine	**Count**	26	11	13
	%	52%	22%	26%

Chart IX: Severity of PONV

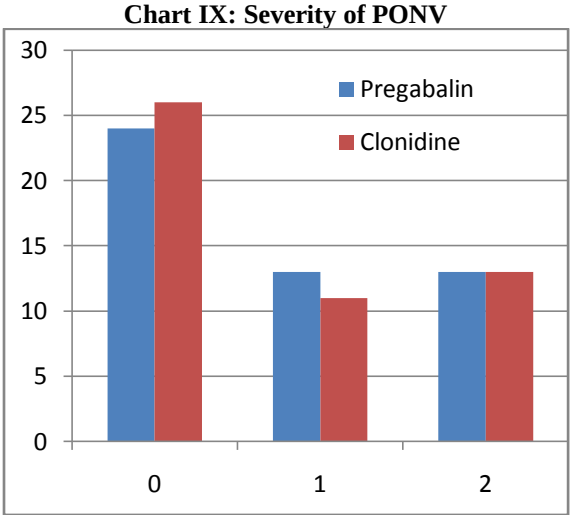


Table 9: Total antiemetic in 24 hours

Groups	Total antiemetic
Pregabalin	**0.52**
Clonidine	**0.56**
p-value	**0.786**

Table 9 shows the total antiemetic requirement in 24 hrs. There is no significant difference in the total antiemetic requirement between the two groups as analyzed by Mann Whitney test.

IV. Discussion

Endotracheal intubation is the gold standard in surgeries under general anaesthesia. Manipulation of the respiratory tract during laryngoscopy and tracheal intubation are associated with adverse haemodynamic and cardiovascular responses including increased catecholamine release leading to increased heart rate, blood pressure, myocardial oxygen demand, dysarythmias[6]. Various drugs have been used over the last few decades to attenuate this haemodynamic stress response. Post operative care requires adequate pain relief for a smooth recovery. PONV is a frequent problem in surgical patients and may lead to patient discomfort and delay in patient discharge. However there is paucity of a single drug that provides haemodynamic stability, analgesia and prevents PONV. In recent times, few drugs like Clonidine and gabapentinoids when used as a premedicant have been found to be useful in achieving all the above goals[7].

Clonidine has haemodynamic, sedative, analgesic and antiemetic effects. Sung et al[8] observed that premedication with oral Clonidine helped to provide Perioperative haemodynamic stability, hence improving the recovery in patients undergoing laparoscopic cholecystectomy. Javaherfroosh F et al[9] analyzed the effect of Clonidine on PONV in laparoscopic gynaelogical surgery and concluded that Clonidine had statistically significant effect in reducing incidence of both nausea and vomiting.

Pregabalin have been used as premedication in various types of surgery and had significant analgesic effect in the postoperative period as a evidenced by lower pain scores as compared to a control drug as in the study conducted by Agarwal et al[10] in a single preoperative dose of Pregabalin 150mg 1 hour before surgery. Schulmeyer et al[11] in 2010 studied the analgesic effects of a single preoperative dose of Pregabalin after laparoscopic sleeve gastrectomy and found that 150mg of Pregabalin given 2 hrs before surgery reduced postoperative pain scores, analgesic consumption and postoperative nausea and vomiting.

Although these drugs have been individually studied, there is paucity of studies comparing the effects of Pregabalin versus Clonidine premedication on the haemodynamic response to laryngoscopy and intubation, analgesia provided and postoperative nausea and vomiting. This study evaluated the efficacy of oral premedication with Pregabalin and Clonidine for attenuation of haemodynamic response to laryngoscopy and tracheal intubation, postoperative nausea and vomiting.

Demographic data like age and BMI were comparable in both the groups. The patients in the study were either ASA class 1 or 2 with no significant history and were equally distributed between the two groups.

The heart rates before induction and before laryngoscopy were comparable in both the groups. The heart rate at laryngoscopy and 1 to 10 minutes following laryngoscopy and tracheal intubation was significantly lower in the Clonidine group as compared to Pregabalin group ($p<0.05$). This may be because Clonidine causes greater attenuation of haemodynamic stress response as compared to Pregabalin. The attenuating effect of Clonidine had been documented by Matot et al[12], Raval et al[13], Passi et al[14] and Singh et al[15]. During their study, they observed the lowest heart rate at 10 minutes after laryngoscopy in Clonidine group.

The mean blood pressure before induction, at laryngoscopy and intubation and upto 4 minutes following endotracheal intubation was lower in Clonidine group but not statistically significant. A significantly lower mean blood pressure was observed at 5, 7, 8, 9 and 10 minutes after laryngoscopy and intubation. Gupta et al[16] in 2011 reported a similar observation that Clonidine was superior to Pregabalin for attenuation of haemodynamic response to laryngoscopy and laparoscopy.

The severity of postoperative pain was assessed by Visual Analog Score (VAS) which have a score ranging from 0 to 10, 0 being no pain and 10 being maximum pain and was recorded both at rest and on coughing. VAS was recorded immediately after the surgery, then every hour for 4 hours, at 8 hours and 24 hours after surgery. At each observation, the number of patients having VAS>3, thereby requiring analgesic was more in Pregabalin group. However, the mean VAS score at rest of all patients at each observation time over 24 hours remained below 3 in both the groups. This indicates that both Clonidine and Pregabalin have analgesic properties which helped in providing basal analgesia and maintain a low VAS score in the postoperative period.

The cumulative analgesic requirement as assessed by the total number of times rescue analgesic was given in 24 hours was significantly lower in the Clonidine group as compared to Pregabalin group (p-value = 0.048). This postoperative analgesia provided by Clonidine in our study was in agreement with analgesic effect of Clonidine reported by Mikawa et al[17] and Sung et al[18].

The severity of PONV was graded on a 3 point scale (0-no nausea and vomiting, 1-nausea, 2-vomitng). In our study, 24 patients in Pregabalin group and 25 patients in Clonidine group have no complain of nausea and vomiting during the 24 hours observation period, while the rest of the patients developed nausea and vomiting and required administration of an antiemetic. However, there was no statistically significant difference in the incidence and severity of PONV between the two groups.

The cumulative antiemetic requirement at 24 hours did not differ significantly in both the groups (p-value=0.786). A decreased in the incidence and severity of PONV by oral Clonidine premedication have been reported by Das et al[19] and Passi et al[20]. Both Clonidine and Pregabalin seems to decrease the incidence of PONV. However, there was no statistically significant difference in the incidence and severity of PONV between the two groups.

V. Conclusion

It is concluded that Clonidine is superior to Pregabalin for attenuation of haemodynamic response to laryngoscopy and endotracheal intubation. Oral premedication in Laparoscopic cholecystectomy with either Clonidine 0.2mg or Pregabalin 150mg attenuate haemodynamic response to laryngoscopy and endotracheal intubation, reduces post operative pain and postoperative nausea and vomiting. Clonidine significantly reduced the requirement of rescue analgesic in the postoperative period. However, there is no significant difference in the incidence and severity of postoperative nausea and vomiting and requirement of rescue antiemetic between the groups.

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