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Comparative study between oral Pregabalin and oral Clonidine in maintaining hemodynamic stability during laparoscopic cholecystectomy under general anaesthesia.

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Abstract—*The aim of the study is to compare the efficacy of orally administered clonidine with respect to Pregabalin in maintaining hemodynamic stability during laparoscopic cholecystectomy under general anaesthesia.*

Materials methods – *After obtaining the institutional ethical approval 68 patients scheduled for elective laparoscopic cholecystectomy were divided into two groups. Group A-34 patients received oral Pregabalin 75mg with 50 ml of water.Group B—34 patients received oral Clonidine 100 mcg with 50 ml of water—30 min before anticipated start time of surgery.Heart rate,Systolic lood pressure(SBP),Diastolic blood pressure(DBP),Mean arterial blood pressure(MBP) were recorded in two groups at different point of time i.e before premedication, before induction, immediately after intubation, 10min,20min after pneumoperitoneum , immediately after release of pneumoperitoneum and immediately after extubation. Incidence of perioperative and postoperative complication in two different groups were also recorded.*

STATISTICAL ANALYSIS*—The results of our observation were compiled , tabulated, and statistically analyzed using chi-square test and unpaired t test as and where applicable.*

RESULTS—*Oral Clonidine was found better than oral Pregabalin in lowering Systolic blood pressure(SBP),Diastolic blood pressure(DBP),Mean arterial blood pressure(MBP)and heart rate changes associated with laryngoscopy, intubation,pneumoperitoneum and extubation. Occurrence of perioperative and postoperative complications in both the group which were mild in nature.*

CONCLUSION—*From observation of the present study it can be concluded that Clonidine(single 100 mcg oral dose) is better agent than oral Pregabalin(single 75 mg oral dose) in maintaining haemodynamic stability during laparoscopic cholecystectomy under general anaesthesia.Adverse effects are minimal for use of the same drugs.*

KEY WORDS*- Clonidine ,Pregabalin, Laparoscopic cholecystectomy,haemodynamic stress response.*

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I. Introduction

Laparoscopic surgery has become the gold standard surgery for the treatment of gallstone disease. The advantages are shorter hospital stay, early ambulation, smaller incisional scar, and less compromised postoperative respiratory and gastrointestinal function. However it is associated with significant intraoperative haemodynamic changes largely due to creation of carbon di oxide pneumoperitoneum to facilitate the surgery. [1]

Laparoscopic cholecystectomy produces immense stress response during laryngoscopy, intubation, during creation of pneumoperitoneum and invariably cause haemodynamic changes associated with increased heart rate, increased blood pressure and associated disturbance of cardiac rhythm. The haemodynamic changes arise mainly due to sympathoadrenal reflex [2] and by release of norepinephrine, epinephrine and vasopressine[3,4] Mechanical effects of pneumoperitoneum, systemic absorption of carbon-di-oxide (CO2) and patient position also contribute to various unfavourable haemodynamic responses. Hypercapnia due to absorption of CO2 causes release of catecholamines[5].Cardiac output is further decreased by reverse Trendelenberg position as well as caval compression due to raised intra abdominal pressure caused by pneumoperitoneum[6].

Several pharmacologic agents have been studied to control this stress response.Centrally acting $\alpha_2$adrenergic antagonist (Clonidine, Dexmedetomidine)[(5,7,8)]β adrenergic antagonist{ Esmolol, Labetolol(alpha and beta blocker}[13],increasd dose of inhalational anaesthetic agents(Sevoflurane, Isoflurane, Miu(μ) receptor agonist (Fentanyl,Remifentanyl[14].NMDA (N-methyl D-aspertate)receptor antagonist (Magnesium

sulphate[15],Gabapentin, Pregabalin[17] have also been studied to control the haemodynamic response during laparoscopic cholecystectomy. They all provide haemodynamic stability during pneumoperitoneum.

Pregabalin is a gabapentinoid. It is structurally related to inhibitory neurotransmitter GABA(Gamma amino butyric acid) and selectively binds to alpha-2(α2) subunit of calcium channel which results in decreased synthesis of glutamate (excitatory neurotransmitter) in Central nervous system(CNS). It posses analgesic, anticonvulsant and anxiolytic activity. It is effective in preventing neuropathic component of acute nociceptive pain.[9,10]

Clonidine is centrally acting alpha adrenergic agonist[5]. It decreases blood pressure and heart rate by reducing plasma level of epinephrine and norepinephrine. Activation of presynaptic receptor in the CNS by α-2 agonist action inhibits sympathetic activity and decreases heart rate ,blood pressure and causes sedation.[5,10,11.]

Review of literature shows only a few studies demonstrating the effectiveness of Clonidine and Pregabalin individually in attenuation of haemodynamic response during laparoscopic cholecystectomy.In view of this observation the present study was framed and was designed to evaluate the efficacy of orally administered Pregabalin and Clonidine in maintaining haemodynamic stability of patients in two different groups undergoing elective laparoscopic cholecystectomy under general anaesthesia.

II. Materials And Methods

After taking proper consent, 68 patients of either sex, aged between 18 and 70 years, ASA(American Society of Anaesthesiology) physical status I and II, posted for elective laparoscopic cholecystectomy under general anaesthesia were included in the study. Unwilling patient,patient incapable of giving consent due to mental or physical illness ,history of uncontrolled hypertension, diabetes mellitus, pregnancy, lactation, ASA physical status III or worse, presence of any absolute contradiction to any of the study drug, body weight beyond 30% of ideal body weight, patients on psychoactive drug, history of alcohol or substance abuse were excluded from the study.

After obtaining the approval for the study from the Institutional ethical committee, informed consent was obtained from all patients. Patients were randomly allocated into one of the two study groups.

Group P:-- 34 patients received oral Pregabalin 75 mg with 50 ml of water, 30 minutes before anticipated start time of surgery.

Group C:- 34 patients received oral Clonidine ,100mg with 50 ml of water,30 minutes before the anticipated start time of surgery.

All the patients were fasted as per ASA guidelines and premedicated with oral Alprazolam 0.25 mg tab plus oral Pantoprazole 40 mg tab, on the night before surgery.

Study drugs were administered 30 min before the anticipated start time of surgery. Before administration of study drugs, each patient's base line heart rate, blood pressure (SBP and MAP) were measured.

Genaral anaesthesia technique:--

All patients were premedicated with IV Glycopyrolate 10 mcg/kg , Ondasetron .08 mg/kg Iv,and Dexamethasone 0.1 mg/kg IV approximately 5 minutes before induction of anaesthesia. On spontaneous ventilation, patient's lung were preoxygenated with 100% oxygen for 3 min, and general anaesthesia was induced with Propofol 2mg/kg Iv administered over 20 second. Endotracheal intubation was facilitated with Succinyl choline 1.5mg/kg IV.Time for laryngoscopy and intubation was limited to 30 seconds. Immediately after completion of tracheal intubation and commencing intermittent positive pressure ventilation, nasogastic tube insertion was performed in all patients. Minute ventilation was adjusted to maintain end –tidal CO_2 between 35 and 40 mm of Hg with peak airway pressure less than 30 cm of H_2O. General anaesthesia was maintained with 15% Isoflurane and 40% Oxygen in nitrous oxide. Surgical muscle relaxation was maintained with loading bolus of 0.5mg/kg Atracurium Besylate IV and 0.1 mg/kg IV at 30 min interval. Intraoperative analgesia was done with inj Tramadol 3mg/kg plus Paracetamol 20mg/kg IV. Ringer lactate solution 500ml IV infusion given initially over 30 min, followed by 100ml/hr IV infusion till the end of surgery was infused to replace fasting fluid deficit and hourly maintenance fluid therapy.

Intra-abdominal pressure was monitored by laparoscopic CO_2 insufflations and maintained at 12 mm of Hg throughout the laparoscopic surgical procedure. All patients were positioned at about 15 degree head-up tilt(reverse-Trendelenberg). At the end of surgery, patients were returned to supine position and residual CO_2 expelled by the surgeon through the laparoscopic ports

At the end of surgery, anaesthetic agents were turned off and patients were assessed for spontaneous return of neuromuscular function. Residual neuromuscular blockade was reversed with Neostigmine 50 mcg/kg plus Glycopyrolate 10 mcg/kg IV given slowly over 3minutes.

Patients were extubated in the operating room after confirmation of appropriate motor response to verbal commands and ability to do sustained head lift for more than 5 seconds.

Heart rate, Systolic, Diastolic and Mean arterial blood pressure were recorded at different point of time i.e before premedication, immediate before induction, immediately after tracheal intubation, 10 min and 20 min

after pneumoperitoneum, and immediately after release of pneumoperitoneum and after extubation in two different study groups.

Intraoperative hypotension (MAP <20% of preoperative), apart from that due to excessive surgical blood loss, was managed with incremental bolus of inj Mephentermine 6 mg IV. If hypotension did not respond to three repeat dose of mephentermine, noradrenaline infusion (100 mcg/ ml) was planned to be started at 3 ml/ hr to maintain the blood pressure. Intraoperative blood loss was managed as per ASA guidelines. Any incidence of bradycardia (Heart rate < 50/min) was treated with inj Atropine 0.6 mg IVIntraoperative hypotension (MAP>30% preoperative) was managed by incremental bolus inj Labetol 5mg IV.

The side effects observed in the form of oxygen desaturation, dry mouth, dizziness, post operative bradycardia in recovery room in patients receiving Clonidine and nausea, dizziness in patients receiving Pregabalin.

III. Result And Analysis

The results of observation thus obtained in each group of patients were tabulated, compiled and statistically analyzed using Microsoft Excel^{TM}2007 for windows and IBM SPSS Statistics ^{TM}version 19 software. Qualitative data(Sex, ASA grade and adverse effects) were compared between groups with chi-square (X^2)test. Quantitative data (age, height ,body weight, BMI, heart rate, systolic blood pressure, diastolic blood pressure, Mean arterial pressure) were compared between groups with unpaired t test. p value <0.05 was considered as statistically significant and p <0.01 was considered as highly significant.

Table 1: Comparison of demographic variables between the study groups:

PATIENT PARTICULARS	GROUP B n = 34	GROUP A n = 34	p VALUE
AGE (years)	47.29± 13.302	45.85±12.013	0.641
SEX(MALE:FEMALE)	13:21	13:21	1
WEIGHT (kg)	61.91±8.12	62.85±8.5	0.642
HEIGHT (cm)	154.67±9.83	156.15±7.17	0.484
BMI (kg/cm2)	25.86±2.054	25.70±2.44	0.817
ASA(I:II)	23:11	23:11	1

*Data are expressed as ratio or x±y where x=mean and y= standard deviation
**Statistically significant when (p< 0.05)
***Statistically highly significant (p<0.01)

Table 2: Comparison of heart rates between the study groups at different points of time:

TIME INTERVAL	GROUP B (mean±SD)	GROUP A (mean±SD)	p VALUE
T1	85.47±13.04	90.24±10.009	0.096
T2	82.14±12.13	91.76±6.57	<0.01
T3	85.15±15.51	96.32±6.50	<0.01
T4	76.85±10.34	108±10.19	<0.01
T5	82.91±18.038	107.76±9.724	<0.01
T6	75.97±11.962	86.94±7.348	<0.01
T7	87.97±14.966	98.85±14.701	<0.01

SD= standard deviation
*Statistically significant when (p< 0.05)
**Statistically highly significant (p<0.01)
***T1= Before pre medication
T2= Immediate before induction
T3= Immediately after tracheal intubation
T4= 10 minutes after pneumo-peritoneum
T5= 20 minutes after pneumo-peritoneum
T6=Immediately after release of pneumo-peritoneum
T7= Immediately after extubation

Table 3: Comparison of systolic blood pressure between the study groups at different points of time

TIME INTERVAL	GROUP B (MEAN ± SD)	GROUP A (MEAN ± SD)	p VALUE
T1	131.24±19.974	125.88±14.304	0.208
T2	125.03±14.534	124.85±14.007	0.959
T3	120.94±12.613	129.59±18.721	0.029
T4	122.50±6.316	147.24±13.878	<0.01
T5	125.09±6.350	139.59±14.258	<0.01
T6	123.76±7.981	122.41±8.023	0.488
T7	131.24±5.516	147.03±14.390	<0.01

SD= standard deviation
*Statistically significant when (p< 0.05)
**Statistically highly significant (p<0.01)
***T1= Before pre medication
T2= Immediate before induction
T3= Immediately after tracheal intubation
T4= 10 minutes after pneumo-peritoneum
T5= 20 minutes after pneumo-peritoneum
T6=Immediately after release of pneumo-peritoneum
T7= Immediately after extubation

Table 4: Comparison of diastolic blood pressure between the study groups at different points of time:

TIME INTERVAL	GROUP B (MEAN ± SD)	GROUP A (MEAN ± SD)	p VALUE
T1	76.21±15.316	75.56±11.519	0.845
T2	78.71±70184	80.97±8.241	0.231
T3	78.35±12.947	88.71±9.634	<0.01
T4	82.74±6.797	100.21±11.047	<0.01
T5	81.68±4.916	87.00±8.341	<0.01
T6	80.62±8.198	81.68±6.966	0.568
T7	80.88±8.538	106.44±12.962	<0.01

SD= standard deviation
*Statistically significant when (p< 0.05)
**Statistically highly significant (p<0.01)
***T1= Before pre medication
T2= Immediate before induction
T3= Immediately after tracheal intubation
T4= 10 minutes after pneumo-peritoneum
T5= 20 minutes after pneumo-peritoneum
T6=Immediately after release of pneumo-peritoneum
T7= Immediately after extubation

Mean arterial pressure

Table 5: Comparison of mean arterial pressure between the study groups at different points of time:

TIME INTERVAL	GROUP B (MEAN ± SD)	GROUP A (MEAN ± SD)	p-value
T1	93.97±15.797	91.82±12.372	0.535
T2	93.79±8.714	95.26±9.980	0.520
T3	92.21±12.426	102±11.916	<0.01
T4	95.79±6.074	115.35±11.203	<0.01
T5	95.97±3.873	104.29±6.717	<0.01
T6	94.53±5.822	95.09±6.639	0.713
T7	97.26±6.653	119.62±5.500	<0.01

SD= standard deviation
*Statistically significant when (p< 0.05)
**Statistically highly significant (p<0.01)
***T1= Before pre medication
T2= Immediate before induction
T3= Immediately after tracheal intubation
T4= 10 minutes after pneumo-peritoneum
T5= 20 minutes after pneumo-peritoneum
T6=Immediately after release of pneumo-peritoneum
T7= Immediately after extubation

Table 6:complications were compared between groups using Mann-Whitney Test.

Complications	Mann-Whitney U	p-value
O2 DESAT	561.000	.317
Airway obs	578.000	1.000
APNEA	578.000	1.000
BRADYPNEA	578.000	1.000
CARDIACARREST	578.000	1.000
NAUSEA	544.000	.154

VOMITTING	578.000	1.000
DRY MOUTH	510.000	.014
HYPOTENSION	578.000	1.000
POST OP BRADY	510.000	.041
HEADACHE	578.000	1.000
DIZZINESS	544.000	.455

*Statistically significant when ($p < 0.05$)
**Statistically highly significant ($p<0.01$)
The incidence of "Dry mouth" and "Post operative bradycardia" in
GroupB were found to be statiscally significant, as p values were found 0.041 in both the cases.

Demographic variable:-- Both the groups were statistically comparable with respect to sex, body weight, height and ASA grading . No significant differences were observed between the groups. (p value> 0.05) [Table 1].

When the heart rates before premedication (T_1) was compared between two groups, no significant difference was found (p value 0.096). The heart rate immediate before induction(T_2) , immediately after tracheal intubation(T_3), 10 min after pneumoperitoneum (T_4), 20min after pneumoperitoneum (T_5), immediately after release of pneumoperitoneum (T_6) and immediately after extubation (T_7) were significantly lower in Group B compared to Group A ($p <0.01$). Group B patients had less heart rate than Group A throughout the study[Table 2]

When systolic blood pressure before induction($T_{1)}$ was compared between two groups, no statistically significant difference was found(p value 0.208). Systolic blood pressure was also similar in both the groups immediately before induction (T_2) (p value 0.959). The systolic blood pressure immediately after tracheal intubation(T_3) was significantly lower in group B(p value 0.029). Similarly systolic blood pressure was significantly lower in Group B than Group A, 10 minutes after pneumoperitoneum(T_4) and 20 minutes after pneumoperitoneum(T_5) (p value <0.01).Again systolic blood pressure was found to be similar in both the groups immediately after release of pneumoperitoneum(T_6)(p value 0.488).But, systolic blood pressure was again significantly lower in Group B immediately after extubation(T_7)(p value <0.01)[Table 3]

The values of diastolic pressure before premedication(T_1) and before induction (T_2) were comparable in both groups with no statistical difference (p values are respectively 0.845 and0.231).Immediately after tracheal intubation(T_3), 10 minute (T_4) and 20 minutes after pneumoperitoneum(T_5) values for Group B was significantly lower than that of Group A (p value<0.01).But values obtained after release of pneumoperitoneum(T_6) were comparable in both the groups without any statistical significance(p value 0.568).Again, diastolic blood pressure was significantly higher in Group A immediately after extubation(T_7)(p value <0.01)[Table 4].

The values of mean arterial pressure before premedication(T_1) and before induction(T_2) were comparable in both groups with no statistical difference.(p values were respectively 0.535 and 0.520).Immediately after tracheal intubation(T_3) ,10 minute (T_4) and 20 min after pneumoperitoneum (T_5), values for Group B was significantly lower than that of Group A(p value <0.01).But values obtained after pneumoperitoneum was comparable in both the groups without any statistical significance(p value 0.713). Again, mean arterial pressure was significantly higher in group A, immediately after extubation(T_7)(p value <0.01)[Table 5].

In Group B, among 34 patient one patient developed oxygen desaturation, which was managed by supplemental oxygen through nasal prong. Four patient complained of dry mouth and three patient complained of dizziness before surgery. Four patients also found to have post operative bradycardia i.e heart rate less than 60 per minute

In Group A, among 34 patients, two patient complained of nausea and five patient complained of dizziness before surgery.

These complications were compared between groups using Mann Whitney Test.

*****Statistically significant when ($p <0.05$)

*Statistically highly significant when ($p <0.01$)

The incidence of" Dry mouth and " post operative bradycardia" in Group B were found to be statistically significant ,as p values were found 0.041 in both cases.

IV. Discussion

Laryngoscopy and endotracheal intubation are associated with rise in heart rate, blood pressure and occasional disturbance in cardiac rhythm[12,13,36,37].Although in normotensive subject these response of blood pressure and heart rate are transient and short lived, they may prove to be detrimental in high risk patients especially in those with cardiovascular disease[15,17]

Similarly creation of pneumoperitoneum during laparoscopic cholecystectomy is also related with adverse hemodynamic responses, such as increase in mean arterial pressure, systemic vascular resistance due to release of vasopressin and catecholamine [3,4].Sympathetic nervous system may also be involved in this pressure responses [2].Laparoscopic cholecystectomy is performed in reverse Trendelenburg position .Cardiac output is further decreased due to decreased venous return caused by above position,as well as caval compression due to raised intra abdominal pressure caused by pneumoperitonium [6].

So effective attenuation of haemodynamic response to laryngoscopy, tracheal intubation, pneumoperitoneum is of great importance in prevention of perioperative morbidity and mortality during laparoscopic cholecystectomy.

Consenting 68 patients of either sex, aged between 18 and 70 years, ASA physical status I and II, posted for elective laparoscopic cholecystectomy under general anaesthesia were selected for the surgery.

The most significant factor influencing cardiovascular response in this study are the duration of laryngoscopy during intubation[16] and intraabdomonal pressure during pneumoperitoneum[17,18,23,21].In the study, the duration of laryngoscopy and intubation were limited to less than 30 seconds and intra-abdomonal pressure was maintained at 12 mm of Hg. Adequate depth of anaesthesia was maintained throughout the surgery.

Clonidine had better effect than Pregabalin in controlling heart rate at all points during the study. Clonidine maintained the heart rate significantly lower (p value<0.01) than Pregabalin from induction to extubation. Kumkum et al[19] and Saxena etal [22] showed that Clonidine decreased pulse rate significantly lower than Pregabalin only during intubation and during creation of pneumoperitoneum, but the effect of Clonidine is not significant after 15 minutes of creation of pneumoperitoneum,and even at the extubation. This may be due to early administration of the drug(90 minutes before premedication), because of which peak effect of Clonidine may be lost at extubation.Parveen et al[23] studied the effect of oral Clonidine versus oral Pregabalin premedication to attenuate pressoe response to direct laryngoscopy in patients undergoing laparoscopic cholecystectomy[23]. Dhiraj et at[20] concluded that Clonidine at dose of 150 mcg attenuated heart rate through out the duration of surgery even at extubation when administered 30 minute before induction.

Clonidine maintained systolic blood pressure at significantly lower value(p value< 0.05) when compared with Pregabalin at various time interval such as immediately after tracheal intubation,10 min,20 min after pneumoperitoneum and at extubation. So,it seems that Clonidine stabilized systolic blood pressure better than Pregabalin whenever there is sympathetic stimulation i.e during laryngoscopy,pneumoperitoneum and extubation. It is also found that at the time of release of pneumoperitoneum ,Pregabalin receiving group had minutely lower systolic blood pressure than Clonidine receiving group.

Unlike systolic blood pressure, patient receiving Clonidine had lower diastolic blood pressure in every time interval throughout the study period than the patient receiving Pregabalin. Diastolic blood pressure attenuating effect of Clonidine was significantly greater (p value<0.01) than that of Pregabalin during intubation,pneumoperitoneum and even at extubation.

Mean arterial pressure is found to be significantly lower(p value<0.01) in Clonidine receiving patient at intubation,upto 20 min after pneumoperitoneum and at extubation. Kumkum et al[19] did not found any significant difference in mean arterial pressure attenuating effect at time of extubation. Asmita et al[21] found similar effect as this study when comparing 150mg Pregabalin and 100mcg Clonidine 30 min before induction.

Serum catecholamine are the most important marker to asses the sympathoadrenal stress response to any stimulus. But in this study, we could not measure its level in every patient due to scarcity of resources regarding serum biochemical tests.This is one of the major limitations of our study.

The side effects observed in form of oxygen desaturation, dry mouth, dizziness,post operative bradycardia in recovery room in patient on Clonidine and nausea, dizziness in patient receiving Pregabalin. The single episode of oxygen desaturation was managed by supplemental oxygen through nasal prong .Other side effects were diminished spontaneously in the post operative period. Kumkum et al[19] in their study found nausea as side effect of both the drugs I,e Pregabalin and Clonidine but they opined it might be due to peritoneal distension due to gas insufflations.Das et al [22] and Dhiraj et al[20] both found Clonidine increased chance of dizziness and dry mouth significantly,But they found that Clonidine decreased incidence of nausea.

V. Conclusion

This prospective, randomized, double blinded study showed that Clonidine at 100mcg single oral dose attenuates haemodynamic stress response in terms of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure better than Pregabalin at 75 mg single oral dose when given as premedication 30 minute before surgery. Dry mouth and post operative bradycardia are two major side effects of Clonidine. But the adverse effect was transient and did not cause any harm to the patients . It was corrected spontaneously.
So, from these observation, we can conclude that Clonidine (single 100 mcg oral dose) is better agent than Pregabalin(single 75mg oral dose) in maintaining hemodynamic stability during laparoscopic cholecystectomy under general anaesthesia.

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