WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 3, 1311-1320. Research Article ISSN 2277– 7105

A PROSPECTIVE RANDOMISED STUDY COMPARING THE PRE-EMPTIVE ANALGESIC EFFECTS OF ORAL GABAPENTIN WITH ORAL CLONIDINE ON INTUBATION RESPONSE AND POST OPERATIVE ANALGESIC REQUIREMENT FOR PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY.

Dr. Kokila[1], Dr. Selvamani[2] and Dr. Juvairiya Banu[3]*

[1]Senior Registrar, Department of Anaesthesiology and Critical Care, Sree Balaji Medical College Hospital, Chennai.

[2]Head of the Department, Department of Anaesthesiology and Critical Care, Sree Balaji Medical College Hospital, Chennai.

*[3]Junior Registrar, Department of Anaesthesiology and Critical Care, Sree Balaji Medical College Hospital, Chennai.

Article Received on
18 Jan. 2017,

Revised on 08 Feb. 2017,
Accepted on 28 Feb. 2017

DOI: 10.20959/wjpr20173-7795

***Corresponding Author**
Dr. Juvairiya Banu
Junior Registrar,
Department of Anaesthesiology and Critical Care, Sree Balaji Medical College Hospital, Chennai.

ABSTRACT

The aim of this study is to compare the effects of Oral Gabapentin and Oral Clonidine as pre-emptive analgesic, on attenuation of the intubation response and postoperative analgesic requirement in patients undergoing Laparoscopic cholecystectomy. In this prospective randomized case control study with respect to a placebo, seventy five patients satisfying the inclusion criteria were randomly divided into three groups of twenty five each. Group A received Gabapentin, Group B received Clonidine, Group C received Placebo of Vitamin C tablet 90 minutes prior to induction. By adding Gabapentin and Clonidine orally 90 minutes preoperatively, it reaches peak concentration in plasma at the onset of surgical stimulus thereby inhibiting central and peripheral neuronal sensitization to pain. Thereby it reduces intubation response, post-operative pain intensity and analgesic prerequisites. Intra-operatively patients were monitored for Heart rate, Systolic blood pressure, diastolic blood pressure and Mean arterial pressure during intubation and post-operatively monitored for sedation, anxiety level, VAS score, total analgesic requirement and RPP (RATE PRESSURE

PRODUCT) for 8 hours. As changes in vital parameters were lower in patients with Oral clonidine, it was found to be slightly better than Gabapentin in attenuating the haemodynamic stress response to laryngoscopy and intubation. Ramsay sedation scores were higher in patients with oral Gabapentine compared to the other two groups, so Gabapentin was found to be slightly better than Clonidine in providing post-operative pain relief.

INTRODUCTION

Laryngoscopy and endotracheal intubation are powerful stimuli which can increase the sympathetic activity leading to tachycardia, hypertension and dysrrythmias. These haemodynamic changes are associated with the release of catecholamines (cortisol and nor-epinephrine), which are prone to get aggravated with laparoscopy using CO2 pneumoperitoneum concomitantly. Pre-emptive analgesia with Gabapentin and Clonidine blunt the stress response to anaesthetic and surgical stimuli, also reduce the narcotic and anaesthetic doses in peri operative period. This feature makes Clonidine or Gabapentin useful in the anaesthetic management of patients undergoing laparoscopic surgeries. Accordingly this study was designed to compare the pre-emptive analgesia of oral Gabapentin and Clonidine in attenuating the haemodynamic response to intubation and decreasing the post-operative pain in patients undergoing laparoscopic cholecystectomy. Gabapentin belongs to the second generation anticonvulsant drugs. It is an inhibitory neurotransmitter, 1-(amino methyl) cyclohexane acetic acid, a structural analog of GABA. Peak plasma concentration is reached in 2 to 3 hours after oral intake. Gabapentin is eliminated from the systemic circulation as unchanged drug in urine and unabsorbed drug is excreted in faeces. Elimination half life is 5-7 hours in normal renal function.

Clonidine, an imidazole derivative of a_2 agonist with antihypertensive effects as well as the ability to potentiate the effects of local anaesthetic agents. The peak concentration is observed in 1 to 3 hours after oral use and maximal hypotensive effect occurs in this duration. Clonidine is 50% metabolized in liver to inactive metabolites. Hydoxylated metabolites undergo secondary conjugation with sulphate or glucoronide and excreted renally. Elimination half life is 9 to 12 hours. Clonidine Oral bolus dose is 4-5mcg/kg and intravenous bolus dose of 4 to 5 mcg/kg and continuous infusion at 2mcg/kg/hour.

Rate Pressure Product also known as Cardiovascular Product or Double Product is used in cardiology and exercise physiology to determine myocardial workload.

Rate Pressure Product(RPP) = Heart Rate(HR) * Systolic Blood Pressure(SBP).

Rate Pressure Product is the stress put on the cardiac muscle based on the number of times it needs to beat per minute(HR) and the Arterial blood pressure it is pumping against(SBP). It will be the direct indication of the energy demand of the heart and thus a good measure of the energy consumption of the heart.

Rate Pressure Product allows you to calculate the internal workload and the haemodynamic response.

HAEMODYNAMIC RESPONSE	RATE PRESSURE PRODUCT
High	More than 30000
High Intermediate	25000 - 29999
Intermediate	20000 - 24999
Low Intermediate	15000 - 19999
Low	10000 - 14999

2. MATERIALS AND METHODS

2.1. Study Design, Inclusion and Exclusion Criteria

After obtaining approval from the Institutional Ethical Committee and the written informed consent from all the patients, the Randomised Clinical study was conducted in RGGGH, in Surgical Gastroenterologist operation Theatre in patients scheduled for elective laparoscopic cholecystectomy under general anaesthesia. Group A received 900mg Tab. Gabapentin, Group B received Tab. Clonidine and Group C received Tab. Vitamin C. The inclusion Criteria were patients between 18-60 years of age, patients with BMI<30kg/m^2 and American Society of Anaesthesiologists physical status 1 and 2 patients, Mallampatti scores 1 and 2 patients and patients posted for elective surgery. Patients with pre-existing conditions were not included namely, patients with history of seizures, renal failure, hepatic failure, known allergy or sensitivity to drugs, patients with ongoing therapy with sustained release opioids, patients with difficult airway and cases which have been converted from laparoscopy to open surgery.

2.2. Randomisation and Study Protocol

The patients satisfying the inclusion criteria were randomly allocated by closed envelope method into 3 groups. Group A (Gabapentin), Group B (Clonidine) and Group C(Placebo). Patients were described about the study methods. In the preoperative room, a good intravenous access was secured and the baseline parameters were noted which includes heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure.

Patients in Group A received tab. Gabapentin 900mg orally, Group B patients received Tab. Clonidine 0.2mg and Group C patients received tab. Vitamin C with sips of water 90 minutes prior to induction. Vital parameters were recorded 3 minutes before induction. After premedication with inj. Glycopyrrolate 0.2mg I.V., INJ. Midazolam 1mg I.V., inj. Fentanyl 2mcg/kg i.v. was given and preoxygenation done. Anaesthesia was induced with inj. Thiopentone 5mcg/kg i.v., or dose adequate to abolish eyelash reflex and followed by a muscle relaxant inj. atracurium 0.5mg/kg i.v. to facilitate laryngoscopy and intubation. Patients were ventilated by mask for 3 minutes using 100% oxygen and sevoflurane 1%. Laryngoscopy and intubation was performed and vital parameters were recorded at the time of intubation and 1,3,5 and 10 minutes after intubation. Maintenance of anaesthesia was carried out using nitrous oxide and oxygen in the ratio of 2:1, sevoflurane 1-2% using controlled ventilation. Patient was observed for complications like hypotension, hypertension, arrhythmias, hypoxaemia and bronchospasm and was treated as required. At the end of the surgery, residual neuromuscular blockade was reversed by inj. Neostigmine 0.05mg/kg and inj. glycopyrrolate intravenously. Immediate post-extubation, vital parameters, sedation scores and anxiety scores were recorded. Patient was shifted to PACU and was monitored for vital parameters for 1,2,4,6 and 8 hours postoperatively. Ramsay Sedation scoring, Anxiety Scoring and side effects like nausea, vomiting and dizziness were recorded.

2.3. Statistical Analysis

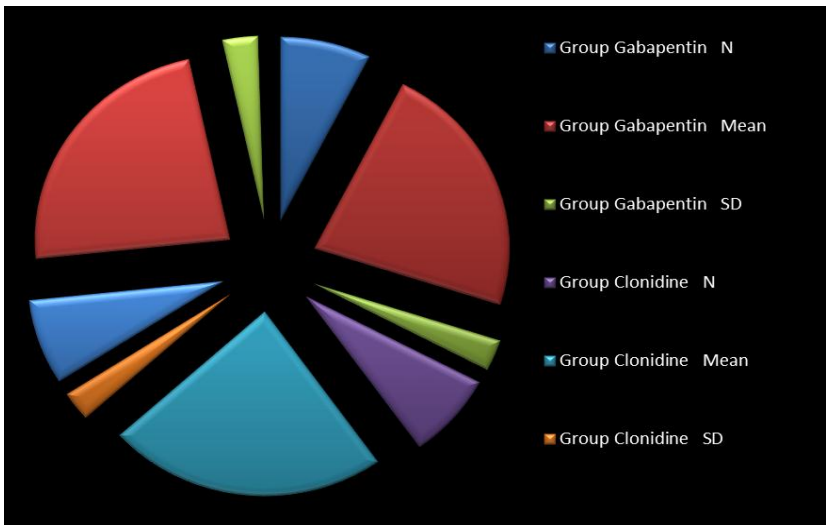
Descriptive Statistics was done for all data and suitable statistical tests of comparison were done. these include the mean and standard deviation (SD) for quantitative variables and category frequency counts for qualitative variables. Next, inferential statistical analysis was undertaken. Continuous variables were analysed with the unpaired t-test and categorical variables were analysed with Chi-square test with Yates correction. Alpha for significance for all inferences was set at $P<0.05$. All tests of hypotheses, wherever applicable, were two-tailed.

2.4. RESULTS

In patients belonging to group Gabapentin, the mean heart rate is 82.67 bpm. In Group Clonidine the mean heart rate is 71.55 bpm. Similarly in group placebo, the mean heart rate is 88.52 bpm. The increase in mean heart rate in group Gabapentin compared to group Clonidine is statistically significant as the p value is 0.0033 as per unpaired t-test. The decrease in mean heart rate measurement in group Gabapentin compared to the group placebo

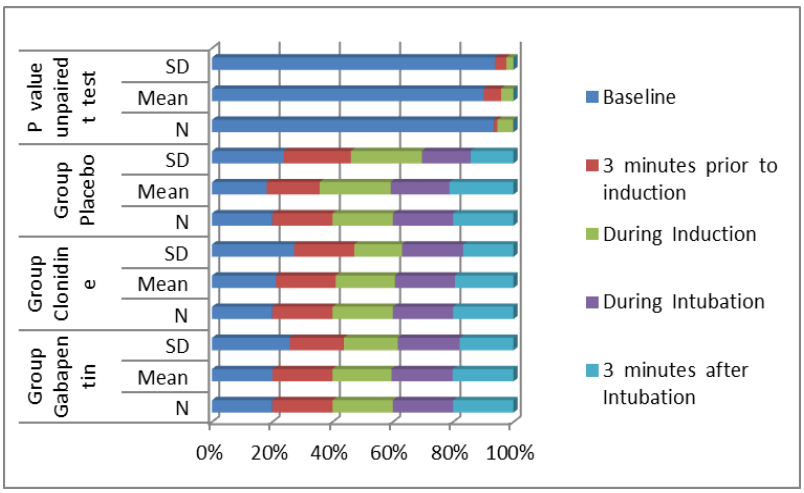
is statistically significant as the p value is 0.0197 as per unpaired t-statistically significant as the p value is 0.0017 as per unpaired t-test indicating a difference among study groups.

Heart rate distribution		**Baseline**	**3 minutes prior to induction**	**During induction**	**During intubation**	**3 minutes after intubation**
Group Gabapentin	N	25	25	25	25	25
	Mean	75.28	73.64	74.52	86.28	96.16
	SD	9.13	4.20	4.85		11.08
Group Clonidine	N	25	25	25	25	25
	Mean	77.44	70.40	69.68	72.52	69.80
	SD	8.60	5.91	4.69	7.19	5.18
Group Placebo	N	25	25	25	25	25
	Mean	77.88	77.64	76.64	85.80	105.24
	SD	9.72	12.76	11.14	6.84	7.24
P value unpaired t test	Group Gabapentine Vs Group Clonidine	0.3936	0.0269	0.0010	0.0000	0.0000
	Group Gabapentin Vs Group Placebo	0.3345	0.0472	0.0393	0.0006	0.0014
	Group Clonidine Vs Group Placebo	0.8661	0.0141	0.0073	0.0000	0.0000

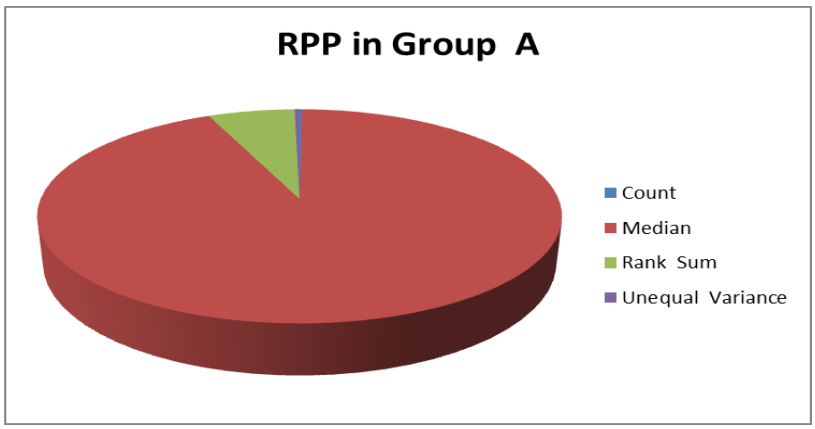


Systolic Blood Pressure Distribution		**Baseline**	**3 minutes prior to induction**	**During Induction**	**During Intubation**	**3 minutes after Intubation**
Group Gabapentin	N	25	25	25	25	25
	Mean	123.60	122.72	120.64	125.36	124.40
	SD	10.89	7.62	7.61	8.72	7.56
Group Clonidine	N	25	25	25	25	25
	Mean	124.72	117.00	116.32	117.04	114.68
	SD	10.68	7.83	6.23	7.95	6.57
Group Placebo	N	25	25	25	25	25
	Mean	124.72	121.24	162.08	134.40	146.36
	SD	10.33	9.66	10.21	6.96	6.22

P value unpaired t test	N	0.7151	0.0090	0.0399	0.0009	0.0000
	Mean	0.7108	0.0459	0.0324	0.0002	0.0000
	SD	1.0000	0.0402	0.0257	0.0000	0.0000



	RPP in Group A	RPP in Group B
Count	25	25
Median	13426	10764
Rank Sum	899	376
Unequal Variance	51	574



	RPP in Group A	RPP in Placebo Group
Count	25	25
Mean	13482.64	20902.16
Median	13426	16530
Rank sum	352	923
Unequal Variance	598	27

	RPP in Group B	RPP in Placebo Group
Count	25	25
Mean	10528.2	20902.16
Median	10764	16530
Rank Sum	325	950
Unequal Variance	625	0

The increase in mean systolic BP in Group Gabapentin compared to Group Clonidine is statistically significant as the p value is 0.0044 as per unpaired t-test indicating a true difference among groups. The decrease in mean systolic BP in Group Gabapentin compared to the group Placebo is statistically as the p value is 0.0382 as per the unpaired t-testing. The decrease in mean systolic BP in Group Clonidine compared to Group Placebo is statistically significant as the p value is 0.0274 as per unpaired t test.

The increase in mean diastolic BP in Group Gabapentin compared to the Group Clonidine is statistically significant as the p value is 0.0203 as per unpaired t test.

The decrease in diastolic BP in Group Gabapentin and Group Clonidine compared to Group Placebo is statistically significant as the p value is 0.0415 and 0.0011 respectively as per the unpaired t test.

The increase in MAP in Group Gabapentin compared to the Group Clonidine is statistically significant as the p value is 0.0065. The decrease in MAP in Group Gabapentin and Clonidine compared Group Placebo is statistically significant as the p values are 0.0478 and 0.0204 as per unpaired t-test.

Ramsay Sedation Score		**Preoperative**	**Post op 0 hour**	**Post op 1st hour**	**Post op 2nd hour**	**Post op 4th hour**	**Post op 6th hour**	**Post op 8th hour**
Group Gabapentin	N	25	25	25	25	25	25	25
	Mean	1.92	2.84	2.64	2.40	1.88	1.64	1.28
	SD	0.76	0.47	0.49	0.58	0.53	0.57	0.54
Group Clonidine	N	25	25	25	25	25	25	25
	Mean	1.28	2.00	1.76	1.68	1.28	1.00	1.00
	SD	0.46	0.58	0.52	0.48	0.46	0.00	0.00
Group Placebo	N	25	25	25	25	25	25	25
	Mean	1.00	1.04	1.12	1.16	1.00	1.00	1.00
	SD	0.00	0.20	0.33	0.37	0.00	0.00	0.00
P value unpaired t test	N	0.0009	0.0000	0.0000	0.0000	0.0001	0.0000	0.0162
	Mean	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0162
	SD	0.0054	0.0000	0.0000	0.0001	0.0054	>0.9999	>0.9999

The increase in Ramsay sedation score in Group Gabapentin compared to Group Clonidine is statistically significant as the p value is 0.0085 as per unpaired t test. The increase in Ramsay sedation score in Group Gabapentin and Group Clonidine compared to Group Placebo is statistically significant as the p value is 0.0396 and 0.0162 as per unpaired t test.

2.5. DISCUSSION

Innumerable anaesthetic techniques have been to proposed to attenuate the stress response to laryngoscopy and intubation, with variable grades of success in acute post operative pain relief. The achievement of good post operative analgesia as a bonus to the smooth induction with negligible reflex haemodynamic response in the course of laryngoscopy and endotracheal intubation remains an important anaesthetic goal. This study was done to assess the pre emptive analgesic effects of two drugs, namely Gabapentin 900mg and Clonidine 0.2mg. These two drugs when given orally, have a role in attenuating the haemodynamic stress response to laryngoscopy and endotracheal intubation and also in decreasing acute post-operative pain relief. Single dose Gabapentin when used as pre treatment prevented development of hyperalgesia and tactile allodynia.

Gabapentin crosses the blood brain barrier readily and its concentration in brain is nearly similar to that present in blood. so, Gabapentin prevented the prevents the peripheral and central sensitization by decreasing hyperalgesia and allodynia associated with surgical manipulation by inhibiting membrane voltage gated calcium channels.

Clonidine is mostly used as an anti-hypertensive drug and has analgesic, sedative and anxiolytic properties. By its central sympatholytic action, it tends to attenuate the haemodynamic response to any surgical stimulus and improve overall peri-anaesthetic cardiovascular stability and central a_2 agonist activity, mediates post operative analgesia.

The drugs were orally administered 90 minutes prior to induction, as the peak action of both the drugs are known to be 1 to 2 hours after oral administration. Variation in heart rate changes decrease with increasing age. marked fluctuations in haemodynamic response are often seen in geriatric patients. To avoid this age related variability, an age range of 18 to 60 years was selected in our study.

In the present study, there were certain changes in all the three groups.

Heart rate changes were lower in patients with oral clonidine as compared to the other two groups. (However, Gabapentin swings were wider than the placebo group.).

Systolic blood pressure, diastolic blood pressure and mean arterial blood pressure changes were lower in patients with oral clonidine compared to the other two groups.

VAS scoring were much lower in patients with oral Gabapentin compared to the other two groups.(Clonidine <Placebo group).

Anxiety scores were higher in patients with oral placebo compared to other two groups (oral Gabapentin>Clonidine).

Ramsay sedation scores were higher in patients oral Gabapentin compared to other two groups. (Clonidine>Placebo).

When comparing all the three groups i.e. Gabapentin, Clonidine and placebo, there was reduction in haemodynamic response with clonidine and gabapentin. This analysis indicates that both Gabapentin and Clonidine have a role in attenuating haemodynamic stress response to larnygoscopy and tracheal intubation and help in maintaining a steady hemodynamic state all throughout the procedure. Similarly, when comparing all the groups, there is significantly decreased need for analgesic requirement in both Gabapentin and Clonidine groups than the Placebo group.

2.6. CONCLUSION

This study demonstrates that a single oral dose of Gabapentin and Clonidine given pre-operatively, effectively reduces intubation response in elective laparoscopic cholecystectomy. Gabapentine is found to be associated with acceptable tachycardia in 2/3rd of this group of patients, persisting for upto 10 to 30 minutes of intubation. Clonidine is found to be more effective in reducing the intubation response compared to both Gabapentin and placebo group. Both Gabapentin and Clonidine when given orally for pre-emptive analgesia, reduced the post-operative pain scores and analgesic requirements in patients undergoing elective laparoscopic cholecystectomy. The incidence of nausea and vomiting was found to be least with Clonidine. Sedation is the only significant side effect observed Gabapentin in our study. Thus from our study and from all findings, Gabapentin and Clonidine drugs were found to be effective as good pre-emptive analgesics in attenuating haemodynamic stress response to laryngoscopy and intubation, with added benefit providing post-operative pain relief also. Clonidine was found to be slightly better than Gabapentin in attenuating haemodynamic stress response to laryngoscopy and intubation. Gabapentine was found to be slightly better than Clonidine in providing post-operative pain relief.

REFERENCES

1. AL-Mujadi H, A-Refai AR, Katzarov MG, Dehrab NA, Batra YK, Al- Qattan AR. (Preemptive Gabapentin reduces post operative pain and opioid demand following thyroid surgery.) Can J Anaesth. 2006; 53: 268-73.
2. Batra YK Indu B, Puri GD: (Attenuation of pulse rate and blood pressure response to laryngoscopy and tracheal intubation by clonidine.) Int Jourl Clin Pharmaco Ther Toxico; 1998; 26: 360-3.
3. Bertrand S, Ng GY, Purisai MG. (The anticonvulsant, antihyperalgesic agent Gabapentin is an agonist in brain G-aminobutyric acid type b receptors negatively coupled to Voltage-dependent calcium channels.|) J Pharmacol Exp Ther 2001; 298: 15-24.
4. Bonhaus DW, Loo C, Secchi R, et al.(Effects of GABA B receptor antagonist CGP 55845 on the anti-convulsant and anxiolytic actions of Gabapentin.) (14th World congress of pharmacology, San Francisco: ASPET). Pharmacologist 2002; 44: A100.
5. Chandrasekara PM and King R. (Attenuation of Cardiovascular responses to endotracheal intubation. Indi Jou Anaes 1984; 32(5): 358-367.
6. Elina M Tiippana et al: ("Do surgical patients benefit from peri operative Gabapentin/ Pregabalin? A Systemic review of efficacy and safety").
7. ANAESTHESIA AND ANALGESIA, vol 104, no.6, 1 June 2007; 104(6): 1545-1556.
8. Fassoulaki A, Melemeni A, Parakeva A, Petropoulos G; (Gabapentin attenuates the pressor responses to direct laryngoscopy and tracheal intubation. Br J Anaes; 2006; 96: 769-73.
9. Fox E, Sklar GS, Hill G, Villanueva R, King BD.(Complication related to the pressor response to endotracheal intubation.) Anaesthesiology, 1977; 47: 524-5.
10. Gee NS, Brown JP, Dissanayake VU, Offord J, ThurlowR, Woodruff GN. (The novel anticonvulsant drug, Gabapentin (Neurotin), binds to the A2D subunit of a calcium channel. J Biol Chem 1996; 271: 5768-76.
11. Ghignone M, quintin L, Duke PC, Kehler CH, Calvillo O (Effects of clonidine on narcotic requirements and haemodynamic response during induction of fentanyl anaesthesia and endotracheal intubation.) Anaesthesiology. 1986 Jan; 64(1): 36-42.