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STUDY OF EFFECTS OF ORAL CLONIDINE ON PREOPERATIVE ANXIOLYSIS AND HEMODYNAMIC PARAMETERS DURING ENDOTRACHEAL INTUBATION IN PATIENTS UNDERGOING ELECTIVE SURGERY

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Abstract
Background: Most patients awaiting elective surgery experience pre-operative anxiety. Anxiety is an unpleasant emotion & may cause patients to avoid planned operation. It may also adversely influence anaesthetic induction & patient recovery. Present study was designed to study of the effects of oral clonidine in preoperative anxiolysis and attenuating hemodynamic responses to endotracheal intubation. **Methodology:** The present study was carried out in 60 patients of ASA I & II physical status aged 18- 60 yrs. scheduled to undergo elective surgery were randomly divided into 2 groups by computer generated randomization chart. Group C received tab clonidine (0.1mg) & Group B received tab vitamin B complex, both received medicines in the waiting room with sips of water 2 hrs. prior to shifting to OT. Preoperative anxiolysis was evaluated using VAS (visual analogue scale) for anxiety. **Results:** The two groups were comparable in terms of demographic variables. Mean VAS anxiety scores significantly reduced in clonidine group when compared to placebo at 2 hrs. after giving the test drug. Statistically significant ($p<0.05$) difference was found between 2 groups in terms of HR, SBP, DBP, and MAP. Mean HR, SBP, DBP and MAP were significantly decreased in clonidine group at all time intervals. **Conclusion:** Oral clonidine (100µg) given 120 min before induction in patients undergoing elective surgeries is effective in attenuating pressor response to laryngoscopy and endotracheal intubation besides providing effective pre-operative anxiolysis.
Keywords: oral clonidine, preoperative anxiolysis, hemodynamic parameters, endotracheal intubation

Introduction

Most patients awaiting elective surgery experience pre-operative anxiety.[1]Anxiety is an unpleasant emotion & may cause patients to avoid planned operation. It may also adversely influence anaesthetic induction & patient recovery.[2] millions of patients receive sedatives to reduce anxiety before surgery but the choice of pre- medication is often determined by habit & tradition rather than by scientific evidence.[3]

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

Although the use of pre-operative benzodiazepines is the most common practice to decrease pre-operative anxiety, they do not have a positive effect on post-operative outcome. Laryngoscopy & intubation are associated with cardiovascular changes such as hypertension, tachycardia, dysrhythmia, increased catecholamines & even myocardial ischaemia.[4]

Several techniques have been proposed to prevent or attenuate these hemodynamic responses such as deepening the plane of anaesthesia, pre-treatment with nitroglycerine, β blockers, calcium channel blockers, opioids etc. Clonidine is a selective central α2 agonist & is a potent antihypertensive drug.[5] Clonidine premedication is known to produce anxiolysis & blunt the stress response to intubation. Hence the present study was designed to study of the effects of oral clonidine in preoperative anxiolysis and attenuating hemodynamic responses to endotracheal intubation.

Material And Methods

This study was a prospective, longitudinal, double-blind study conducted in the Department of Anesthesiology at Anandrishiji Hospital and Medical Research Centre, Ahmednagar, Maharashtra, India, over two years from August 2020 to July 2022. The study received approval from the institutional ethical committee.

Inclusion Criteria

- Patients of either gender, aged between 20 and 60 years, belonging to ASA grades I or II, body weight 40 to 60 kg, scheduled for various elective surgeries under general anesthesia, who provided written informed consent.

Exclusion Criteria

- Patients with a history of asthma, increased intracranial pressure, congestive heart failure, valvular heart disease, coronary artery disease, on concomitant Monoamine Oxidase inhibitors, with history of coagulation disorders, known hypersensitivity to any drugs being used, hypotension or hypovolemic shock, known cases of hypertension under treatment, any respiratory illness.

Patients underwent a preanesthetic check-up prior to the day of surgery, assessed by history and clinical examination. Visual analogue anxiety scores (VAS: 0 = no anxiety, 100 = worst imaginable anxiety) were explained to them. On the day of surgery, VAS anxiety scores were assessed in the waiting room before (baseline) and 2 hours after administration of the test drug (just before transferring to the operating theatre).

In the waiting room, patients' heart rate, blood pressure (systolic, diastolic, and mean arterial pressure), respiratory rate, and SpO2 were recorded as pre-operative values using a multiparameter monitor.

Randomization and Blinding Randomization was achieved using a computer-generated chart.

- Group C received 0.1 mg clonidine.
- Group B received a vitamin B complex tablet. Both were administered 2 hours prior to transfer to the operating theater, with the patients and anesthesiologists blinded to the treatment group. Recordings were made by a resident anesthesiologist who was also unaware of the group allocation.

Upon entering the operating room, an 18G catheter was inserted for IV access and Ringer lactate solution was started. Monitoring of non-invasive blood pressure (NIBP), heart rate, electrocardiogram, and arterial oxygen saturation was initiated.

Anesthesia Induction and Monitoring

- T0: After a 3-minute preoxygenation period, anesthesia was induced with intravenous thiopentone (5 mg/kg) and succinylcholine (1.5 mg/kg) to facilitate endotracheal intubation, performed by an experienced anesthetist.
- T1: Time of laryngoscopy.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

- T2: 1 minute post-intubation.
- T3: 3 minutes post-intubation.
- T4: 5 minutes post-intubation.
- T5: At skin incision.

Anesthesia was maintained using 67% N2O in 33% O2 and 0.5% halothane, with controlled ventilation. Intraoperative analgesia was provided using 0.3 mg/kg pentazocine. Residual neuromuscular blockade was reversed at the end of surgery with 0.05 mg/kg neostigmine and 0.1 mg/kg glycopyrrolate administered intravenously.

Data Analysis Data were analyzed using SPSS V15.0, presented as mean ± SD, and N for continuous data, with number and percentage for categorical data. The means of the two groups were compared using Student's unpaired t-test for numerical data, and Fisher's Exact Probability tests for categorical data. All tests were two-tailed, with a significance level (α) set at P<0.05.

Results

The two groups were comparable in terms of demographic variables such as age, gender, body weight.

Table 1: General characteristics

Characteristics	GROUP C (n=30)	GROUP B (n=30)
Mean Age (in years)	44.67 ± 5.62	44.93 ± 4.13
MEAN WEIGHT (in kgs)	50.66 ± 5.36	54.16 ± 5.6
Gender		
Males	10 (33.3%)	7 (23.3%)
Females	20 (66.7%)	23 (76.7%)

Mean VAS anxiety scores significantly reduced in clonidine group when compared to placebo at 2 hrs. after giving the test drug. Significant (P<0.05) difference between 2 groups at 2 hrs. after taking drug.

Table 2: Comparison of Mean VAS anxiety score between 2 groups

Mean VAS anxiety score	GROUP C (n=30)	GROUP B (n=30)	Test statistic, Significance, P value
Before drug (baseline)	68.37 ± 8.36	69.03 ± 5.65	t=0.4, NS,P=0.7
Before shifting to OT (2 hrs. after taking drug)	37.40 ± 3.41	56.27 ± 7.00	t= 13.3, S,P<0.001

45.30% reduction in GROUP B was 18.5% and in GROUP C it was 45.3% Significant (P<0.05) reduction in mean VAS anxiety scores for both groups.

Table 3: Intragroup comparison of VAS anxiety scores

	GROUP C n = 30				GROUP B n = 30			
	Mean ± SD	Diff from BL	% diff	P value	Mean ± SD	Diff from BL	% diff	P value
Before giving drug (baseline)	68.37 ± 8.36				69.03 ±5.65			
Before shifting to OT (2 hrs. after taking drug)	37.40 ± 3.41	30.97	45.30%	<0.001	56.27 ±7.00	12.76 ± 7.90	18.50%	<0.001

Significant (P<0.05) difference in Mean HR at all time points between 2 groups.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

Table 4: Comparison of mean HEART RATE (HR) between 2 groups

Group	GROUP C	GROUP B	Comparison between 2 groups
After a stabilization period of 3 min. - baseline (T0)	91.87 ± 3.87	96.20 ± 9.40	t = 2.3, S,P=0.023
At the time of laryngoscopy (T1)	90.53 ± 3.31	98.20 ± 9.62	t = 4.1, S,P<0.001
1 min. after intubation (T2)	89.97 ± 3.28	99.13 ± 7.62	t = 6.1, S,P<0.001
3 min. after intubation (T3)	89.07 ± 3.26	100.37 ± 9.36	t = 6.3, S,P<0.001
5 min. after intubation (T4)	90.27 ± 2.74	100.93 ± 9.80	t = 5.7, S,P<0.001
At skin incision (T5)	94.03 ± 2.94	106.50 ± 9.25	t = 7.0, S,P<0.001

Significant (P<0.05) difference in Mean SBP at all time points between 2 groups.

Table 5: Comparison of mean SYSTOLIC BLOOD PRESSURE (SBP) between 2 groups

Group	GROUP C	GROUP B	Comparison between 2 groups
After a stabilization period of 3 min. - baseline (T0)	122.63 ± 7.02	136.80 ± 11.96	t = 5.6, S,P=0.023
At the time of laryngoscopy (T1)	115.90 ± 5.36	134.83 ± 12.71	t = 7.5, S,P<0.001
1 min. after intubation (T2)	112.67 ± 7.02	135.47 ± 13.69	t = 8.4, S,P<0.001
3 min. after intubation (T3)	112.63 ± 5.87	134.90 ± 11.88	t = 9.2, S,P<0.001
5 min. after intubation (T4)	117.30 ± 5.88	134.30 ± 10.8	t = 7.6, S,P<0.001
At skin incision (T5)	124.40 ± 5.77	146.27 ± 14.15	t = 7.8, S,P<0.001

Significant (P<0.05) difference in Mean DBP at all time points between 2 groups.

Table 6: Comparison of mean DIASTOLIC BLOOD PRESSURE (DBP) between 2 groups

Group	GROUP C	GROUP B	Comparison between 2 groups
After a stabilization period of 3 min. - baseline (T0)	80.63 ± 3.49	89.07 ± 6.62	t = 6.2, S,P<0.001
At the time of laryngoscopy (T1)	78.57 ± 2.98	88.27 ± 7.56	t = 6.5, S,P<0.001
1 min. after intubation (T2)	78.1 ± 3.06	89.67 ± 6.72	t = 8.6, S,P<0.001
3 min. after intubation (T3)	78.17 ± 3.13	87.9 ± 7.50	t = 6.6, S,P<0.001
5 min. after intubation (T4)	80.1 ± 4.51	88.03 ± 5.78	t = 5.9, S
At skin incision (T5)	82 ± 3.33	89.27 ± 7.04	t = 7.2, S,P<0.001

Significant (P<0.05)difference in Mean MAP at all time points between 2 groups.

Table 7: Comparison of MEAN ARTERIAL PRESSURE (MAP) between 2 groups

Group	GROUP C	GROUP B	Comparison between 2 groups
After a stabilization period of 3 min. - baseline (T0)	94.3 ± 4.15	104.7 ± 8.11	t = 6.3, S,P<0.001
At the time of laryngoscopy (T1)	90.7 ± 3.41	103.5 ± 9.08	t = 7.2, S,P<0.00 1
1 min. after intubation (T2)	89.3 ± 3.55	104.47 ± 8.41	t = 9.1, S,P<0.001
3 min. after intubation (T3)	89.33 ± 3.26	103.13 ± 8.24	t = 8.5, S,P<0.001
5 min. after intubation (T4)	92.13 ± 4.63	103.23 ± 7.01	t = 7.2, S,P<0.001
At skin incision (T5)	95.77 ± 3.60	109.87 ± 8.66	t = 8.2, S,P<0.001

No Significant (P>0.05) difference in Mean SPO2 at all time points between 2 groups.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

Table 8: Comparison of mean SPO2 between 2 groups

Group	GROUP C	GROUP B	Comparison between 2 groups
After a stabilization period of 3 min. - baseline (T0)	99.83 ± 0.46	99.87 ± 0.43	t =0.3, NS,P=0.8
At the time of laryngoscopy (T1)	99.83 ± 0.46	99.87 ± 0.43	t =1.0, NS,P=0.3
1 min. after intubation (T2)	99.87 ± 0.43	99.83 ± 0.53	t =0.3, NS,P=0.8
3 min. after intubation (T3)	99.97 ± 0.18	99.87 ± 0.43	t =1.2, NS,P=0.3
5 min. after intubation (T4)	99.87 ± 0.43	99.8 ± 0.55	t =0.5, NS,P=0.6
At skin incision (T5)	99.93 ± 0.25	99.87 0.43	t =0.7, NS,P=0.5

No Significant (P>0.05) difference in Mean RR at all time points between 2 groups.

Table 9: Comparison of mean Respiratory Rate (RR) between 2 groups

Group	GROUP C	GROUP B	Comparison between 2 groups
After a stabilization period of 3 min. - baseline (T0)	15 ± 0.91	14.83 ± 0.87	t =0.7, NS,P=0.5
At the time of laryngoscopy (T1)	15.07 ± 0.83	14.73 ± 0.77	t =1.6, NS,P=0.1
1 min. after intubation (T2)	14.93 ± 0.87	14.83 ± 0.59	t =0.5, NS,P=0.6
3 min. after intubation (T3)	14.9 ± 0.80	15 ± 0.83	t =0.5, NS,P=0.6
5 min. after intubation (T4)	14.83 ± 0.83	15.2 ± 0.87	t =1.7, NS,P=0.1
At skin incision (T5)	15.17 ± 0.83	15± 0.91	t =0.7, NS,P=0.5

Discussion

Preoperative anxiety is an important problem because it produces undesirable effects on anaesthesia & perioperative outcome. It not only changes doses of drugs which are needed for induction, maintenance of anaesthesia, recovery from anaesthesia, but also it affects psychological condition of patients.

We used 0.1mg oral clonidine and found effective pre- operative anxiolysis. Mahajan RK *et al.*,[6] conducted as a single blind trial on 60 children to study the effects of oral clonidine and oral midazolam as a preoperative anxiolytic agent. They concluded that a satisfactory anxiolysis was achieved with both (P>0.05), but the quality of the anxiolysis was better with clonidine (P<0.05) and hence concluded that oral clonidine is a good alternative to oral midazolam as a premedication in children.

Saini V *et al.*,[7] noted that, patients receiving clonidine had less subjective anxiety (p<0.01) which persisted intraoperatively as compared to patients who received placebo. Khan AA *et al.*[13] observed a significant decrease in anxiety in the clonidine group as compared to pregabalin group. They found that out of 40 patients 37(92.5%) patients became quiet and comfortable (score 0) 120 min after clonidine where only 1(2.5%) patient scored 1 before giving clonidine.

Several investigators have used different scales for measuring pre-operative anxiety i.e., STAI, VAS, 5-point scale. We used VAS scale because it is easy to assess and reliable. We compared mean VAS scores and found no significant difference between 2 groups at Baseline values. However, we noted a significant (P<0.05) difference between 2 groups at 2 hrs. after taking drug.

Laryngoscopy & intubation can cause striking changes in hemodynamic probably as a result of intense sympathetic nervous system responses to stimulation. However, in most patients these changes are transient, highly variable, and probably of little consequence. In patients who are at risk for developing increased intracranial pressure, arterial hypertension or

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

myocardial ischemia, these changes may be life- threatening.

Sharma V *et al.*,[8] compared the efficacy of oral clonidine 0.3 mg and oral gabapentin 900 mg as a premedication and found that using clonidine or gabapentin, one can effectively provide stable hemodynamic conditions during laryngoscopy and endotracheal intubation, but more so with clonidine. They observed a decreased pressor response with clonidine as compared to gabapentin. Although it was statistically insignificant but it was observed clinically and hence noted. When compared to placebo, clonidine significantly reduced HR, SBP, DBP, and MAP for the study period.

In study by Arshi *et al.*,[9] differences in systolic blood pressure between the two groups were significant at three subsequent measurements following intubation so were the differences in the heart rates (P=<0.001) statistically significant difference were observed between control and clonidine group in the anxiety score.

Tabeli H *et al.*,[10] performed a randomized controlled trial to evaluate the efficacy of pre-anaesthetic orally administration of clonidine (0.2 mg) on pulse rate and blood stress response to laryngoscopy and tracheal intubation. The Clonidine group showed a significant superiority over placebo in the prevention of increase in systolic blood pressure as well as heart rate over the intubation.

Sridhar CB *et al.*,[11] conducted a randomised double-blind study and found that low dose (100µg) oral clonidine is a very efficient, easy to administer and cost-effective premedication drug during laparoscopic procedures Low dose oral clonidine(100mcg) is an efficient cardiovascular modulator when given as premedication in patients undergoing laparoscopic surgeries. Low dose oral clonidine (100mcg) is an efficient cardiovascular modulator when given as premedication in patients undergoing laparoscopic surgeries.

In our study conducted with oral clonidine (0.1mg) stable hemodynamic are seen. We also used "0.1mg" clonidine and found it to be effective in attenuation of hemodynamic responses.

A variable combination of drugs used for premedication, induction, relaxation and maintenance of anaesthesia can influence the sympathetic response to laryngoscopy and intubation. Midazolam i.v decreases the blood pressure and increases the heart rate similar to thiopentone. Pentazocine an opioid agonist antagonist may increase the blood pressure, heart rate and catecholamine levels.[12] Glycopyrrolate premedication can moderately increase the heart rate. So, we omitted these premedication drugs in our study & this should not be a concern in ASA 1 & 2 patients. Nevertheless, we observed increased lacrimation & secretions (though we did not formally record in observations) in the endotracheal tube after induction as we skipped anti-sialagogue & analgesic premedication. Thiopentone was selected for induction since it still continues to be the most popular agent for induction. In normovolemic patients" thiopentone 5mg/kg i.v can transiently decrease 10-20mm Hg of blood pressure and increase the heart rate by 15-20 beats/min.

Succinylcholine has negative inotropic and chronotropic effect. It acts on the muscarinic receptors of SA node. A marked noradrenergic response was noted when intubation was performed under succinylcholine. However, the unique intubating conditions obtained from succinylcholine cannot be provided by any other muscle relaxant & succinylcholine is the muscle relaxant which we routinely use in our institution. Hence, we used it for intubation in our study.

Nitrous oxide may increase the tone of sympathetic nervous system. The direct action of nitrous oxide is negative inotropism which is offset by increased sympathetic tone. Halothane has potency to decrease the heart rate but at concentrations used for maintenance it does not appreciably change the heart rate. However, all inhalation agents were given only after the study period. Surgery was commenced only after the study period i.e. 5 min after intubation.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

The most significant laryngoscopic factor influencing cardiovascular responses is found to be the duration of laryngoscopy. A linear increase in heart rate and mean arterial pressure during the first 45 seconds has been observed.

Limitations of Study:

1. Sample Size and Single-Center Data: Conducted at a single center with a limited sample size of 60 patients, the findings may not be generalizable to other settings or wider populations. Different hospitals have varying levels of care, patient demographics, and procedural norms, which can influence outcomes significantly.
2. Subjectivity in measurement of pre-operative anxiety measurements: In present study no objective measurement of pre-operative anxiety was done. This variation can impact the reliability of comparisons between group C and group B.
3. Duration of laryngoscopy - Though we restricted our laryngoscopy period to less than 15 seconds, we did not measure the exact duration of laryngoscopy. However, it is not possible to do laryngoscopy and intubation within 15 seconds.
4. Exclusion of Certain Patient Populations: This selection criterion may limit the study's applicability to all postoperative patients, particularly those with more complex medical backgrounds or those at higher risk of respiratory complications.

Conclusion

Oral clonidine (100μg) given 120 min before induction in patients undergoing elective surgeries is effective in attenuating pressor response to laryngoscopy and endotracheal intubation besides providing effective pre-operative anxiolysis. As per our study, since there is a statistically significant difference between clonidine and placebo groups, we can safely conclude that oral clonidine is an effective premedication for preoperative anxiolysis and for attenuation od hemodynamic pressor responses following laryngoscopy and endotracheal intubation.

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