A COMPARATIVE CLINICAL EVALUATION OF ORAL CLONIDINE VS. PREGABALIN PREMEDICATION FOR ATTENUATION OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY AND INTUBATION- A PROSPECTIVE RANDOMISED DOUBLE BLINDED PLACEBO-CONTROLLED STUDY

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ABSTRACT

BACKGROUND

Endotracheal intubation is considered gold standard in patients undergoing general anaesthesia. Direct laryngoscopy and tracheal intubation result in an increase in blood pressure and heart rate, the so called 'pressor response'. Various techniques and drugs have been used in the past to attenuate the pressor response, however none has been proved to be ideal. We conducted this study to compare any possible blunting of cardiovascular effects of laryngoscopy and tracheal intubation by the use of 150 mg pregabalin or 200mcg clonidine with the group that did not receive any of the two drugs.

MATERIALS AND METHODS

90 ASA Grade 1 and 2 patients aged 18-60 years of both genders were recruited for the study with 30 patients in each group.
Group A – Received oral pregabalin 150 mg with sip of water 120 min before the surgery.
Group B – Received oral clonidine 200 mcg with sip of water 120 min prior to surgery.
Group C – Oral placebo (multivitamin) with sip of water 120 min prior to surgery. On arrival in the operating room, HR, SBP, DBP, MAP were recorded at baseline, after induction, 1-, 3-, 5- and 10-mins after laryngoscopy and intubation.

RESULTS

In this study, there was a significant reduction in HR, SBP, DBP, MAP after laryngoscopy and intubation in pregabalin and clonidine group in comparison to control group. Oral premedication with pregabalin as well as clonidine attenuates the haemodynamic response to laryngoscopy and intubation with clonidine being superior to pregabalin.

KEYWORDS

Laryngoscopy, Intubation, Haemodynamic Changes, Pregabalin, Clonidine.

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BACKGROUND

Endotracheal intubation is considered to be the gold standard in patients undergoing surgery requiring general anaesthesia. Direct laryngoscopy and tracheal intubation result in an increase in blood pressure and the heart rate, the so called 'pressor response'.[1] This reflex response might be of short duration and of little consequences in majority of patients, but can cause serious complications in patients with underlying abnormalities such as coronary artery disease, reactive airways or intracranial neuropathology.[2] Various techniques and drugs have been used to attenuate the circulatory response due to laryngoscopy and tracheal intubation during general anaesthesia. However, no apparent consensus has been reached on which method is ideal to abolish or attenuate these reflex hemodynamic changes'.

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Perioperative care requires anxiolysis, intraoperative haemodynamic stability, adequate pain relief and control of postoperative nausea and vomiting. However, there is paucity of drugs that are useful in achieving all the above goals.

α2 adrenoceptor agonist (clonidine) and gabapentinoids (gabapentin and pregabalin) may provide an alternative method. Clonidine is an α2 adrenoceptor agonist with sedative and analgesic effects, it has also been shown to have beneficial effects of blunting the hemodynamic

responses to laryngoscopy and tracheal intubation.[3] Clonidine, a centrally acting antihypertensive agent, known to reduce central sympathetic outflow and modulate presynaptic transmitter release, has been shown to suppress central noradrenergic hyperactivity induced by immobilization stress in animals,[4] to decrease the MAC of halothane and the dose of narcotics required to prevent reflex cardiovascular response to laryngoscopy and tracheal intubation.[5] Gabapentin is an anticonvulsant that has antinociceptive and antihyperalgesic properties.[6] Pregabalin is a newer gabapentinoid that has been found to possess anxiolytic, analgesic and antiepileptic activity.[7] Pregabalin is currently used for the treatment of neuropathic pain, fibromyalgia etc.[8] it is being evaluated as a premedicant to help attenuating the hemodynamic response to laryngoscopy and intubation.

MATERIALS AND METHODS

After obtaining the approval from the hospital ethics and scientific committee and written informed consent from all patients, study was conducted.

Study Population

Patients posted for elective surgery under general anaesthesia (GA).

Study Design

Prospective, double-blind, randomized, placebo-controlled study.

Sample Size

90 ASA Grade 1 and 2 patients (30 in each group).

Sampling Technique

Randomisation was done by a computer-generated allocation schedule using allocation concealment to prevent prior knowledge of treatment assignment. To decrease bias and confounders the decision to accept or reject a participant was made using inclusion and exclusion criteria. Informed consent was obtained from participants prior to obtaining the randomization code. For purposes of statistical blinding, study identification number for group A, group B, group C were allocated by the statistician according to the randomization number and the same was entered in the data collection form.

Inclusion Criteria

Age 18-60 years of either sex, ASA grade 1 and 2, elective surgical procedure requiring general anaesthesia and endotracheal intubation.

Exclusion Criteria

Patient refusal, anticipated difficult airway, BMI>30, patients with low pulmonary compliance or high airway resistance, patients with history of cardiovascular disease, long standing medical(hepatic or renal) disease, history of alcohol use, drug abuse, patients taking pregabalin, gabapentin, benzodiazepine or antidepressant drugs.

Methodology

A detailed preanaesthetic evaluation including all routine investigation was carried out in all patients. Age, sex and body mass index of all patients were recorded. All patients were kept fasting as per the ASA guidelines. All patients were given Tab. Alprazolam 0.25 mg one night before the surgery. Written and informed consent was taken from the patients in a language which they understand.

Group A: Cap. Pregabalin 150 mg orally with a sip of water 120 min prior to surgery.

Group B: Tab. Clonidine 200 µg orally with a sip of water 120 min before the surgery.

Group C: Placebo (multivitamin) orally with a sip of water 120 min prior to surgery.

Anaesthetic Technique

All patients were received in the preoperative area. On arrival in the operative room, monitoring of NIBP, SBP, DBP, MAP, HR, ECG, SPO2 were recorded(baseline). Then the patient was given Inj. Ondansetron 0.1 mg/kg body weight, Inj Midazolam 0.02 mg/kg body weight intravenously. A uniform anaesthetic technique was used in all the patients. All patients were preoxygenated with 100% O_2 for 3 minutes. Inj. fentanyl 2 µg/kg followed by Inj. Propofol 2 mg/kg was used for induction, Sevoflurane (2-3%) and 66% N2O in O_2 and neuromuscular blockade was achieved with Inj. Atracurium 0.5 mg/kg after being bled to ventilate. Bag and mask ventilation was done for 3 minutes followed by laryngoscopy and tracheal intubation using orotracheal cuffed tube of appropriate size by an experienced anaesthetist using the Mackintosh laryngoscope. Anaesthesia was maintained with sevoflurane (1.5-2%) and 66% N_2O in O_2 and Inj. Atracurium.

HR, SBP, DBP, MAP were recorded at baseline, after induction, 1 minute after intubation, 3 minute after intubation, 5 minute after intubation, 10 minute after intubation and then at 10 min interval for 2 hrs or till the completion of surgery whichever was earlier. No stimulus was applied during the initial 10 minutes.

Any fall in MAP and HR more than 20% from baseline was treated with pressor agents (inj. Mephentermine 3-6mg iv) and inj. Atropine 0.3 mg iv. These patients were excluded from the study and extra patients were recruited to make 30 in each group.

Statistical Analysis

$P<0.05$ was considered to be significant. All data was statistically analysed using STATA 9.0 software. Normally distributed data were reported as means (SD) and will be evaluated by ANOVA and t-test assumed. Categorical data will be compared using Fisher's exact test or chi-square test.

RESULTS

- Demographic data were comparable in all three groups.
- Male and Female ratio was comparable in all three groups (p value-0.487).

- Mean age was comparable in all three groups (p value -0.434).
- ASA grading was comparable in all three groups (p value-0.124).
- Time of laryngoscopy and intubation was comparable in all three groups (p value-0.814).

BMI was comparable in all three groups (p value – 0.990).

Time of Laryngoscopy and Intubation and Duration of Surgery

As shown in figure 1, the 90 patients included in the study were comparable with respect to time taken for intubation (p value 0.814).

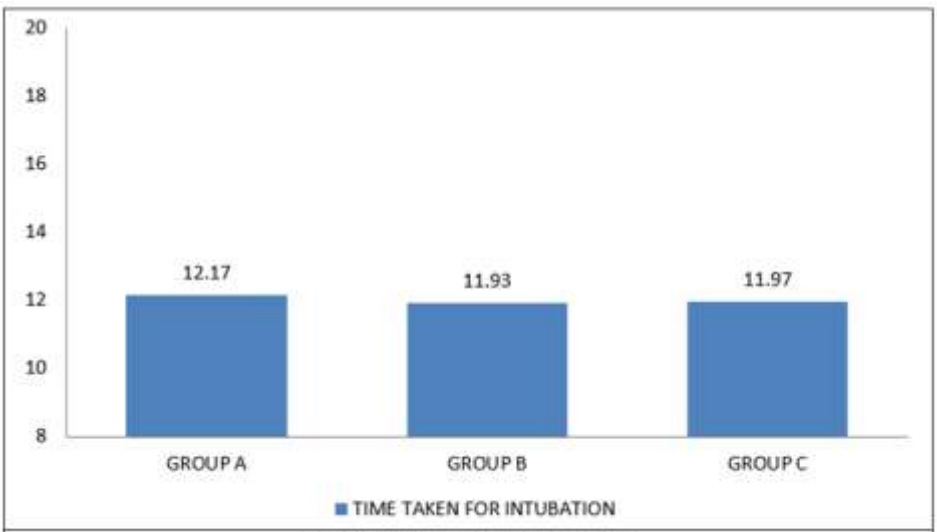

Figure 1. Time Taken for Intubation

- **Heart Rate**

As shown in table 1 and figure 2, changes in heart rate were statistically significant in premeditated groups at baseline, after induction, 1, 3, 5 and 10 min after laryngoscopy and intubation (p value<0.05) as compared to control group. Between the two drugs pregabalin and clonidine, there was increase in HR at 1, 3 min after laryngoscopy and intubation, however in clonidine group the increase was less. As compared to pregabalin, clonidine is better in decreasing the heart rate which was statistically significant after induction (p value-0.013) and 10 min post laryngoscopy and intubation (p value< .001).

Groups (n=30)	Baseline	After Induction	1 min AI	3 min AI	5 min AI	10 min AI
Group A	84±10.629	80.7±9.502	89.17±10.767	87.13±11.24	83.6±10.611	82.13±11.13
Group B	80.5±14.724	73.9±10.889	86.33±16.707	82.73±12.774	78.5±11.129	70.07±9.65
Group C	89.63±12.491	92.57±14.304	101.07±14.612	96.53±11.999	91.47±13.122	85.97±13.10
p Value	0.023	<0.001	<0.001	<0.001	<0.001	<0.001
p Value b/w Group A and Group B	0.296	.013	0.438	0.162	0.074	<0.001

Table 1. Mean Heart Rate

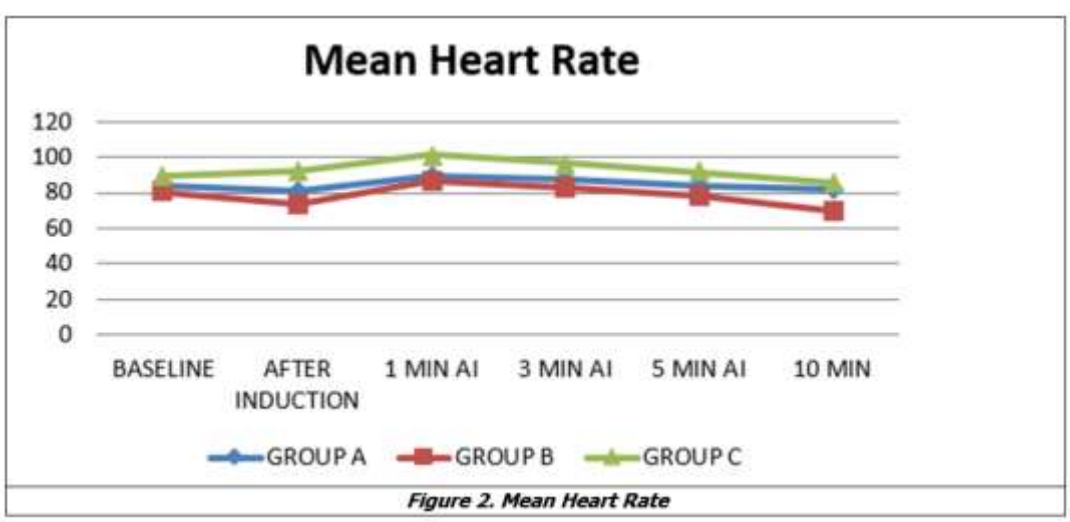

Figure 2. Mean Heart Rate

- **Blood Pressure**

  Systolic Blood Pressure (SBP)- As shown in table 2 and figure 3 SBP was comparable at baseline in the three groups. Changes in SBP was statistically significant in premedicated groups after induction, 1, 5, 10 min following laryngoscopy and intubation (p value<0.05) in comparison to placebo group. Between the two drugs pregabalin and clonidine, clonidine caused a greater reduction in SBP in comparison to pregabalin group after induction, 1, 3, 5, 10 min after laryngoscopy and intubation which was statistically significant after induction (p value<0.05) and 10 min post laryngoscopy and intubation (p value<0.001).

Groups (n=30)	Baseline	After Induction	1 min AI	3 min AI	5 min AI	10 min AI
Group A	124.60±15.26	112.03±17.49	123.77±20.45	114.90±17.387	111.47±15.971	111.67±14.440
Group B	127.27±13.68	100.21±14.199	122.6±21.08	114.80±15.880	104.60±11.125	94.47±7.422
Group C	125.63±13.37	123.03±24.594	142.00±21.1	123.77±16.55	115.20±18.91	114.30±14.53
P value	0.763	<0.001	0.001	0.062	0.034	<0.001
p Value b/w Group A and Group B	0.0479	0.006	0.829	0.982	0.058	<0.001

Table 2

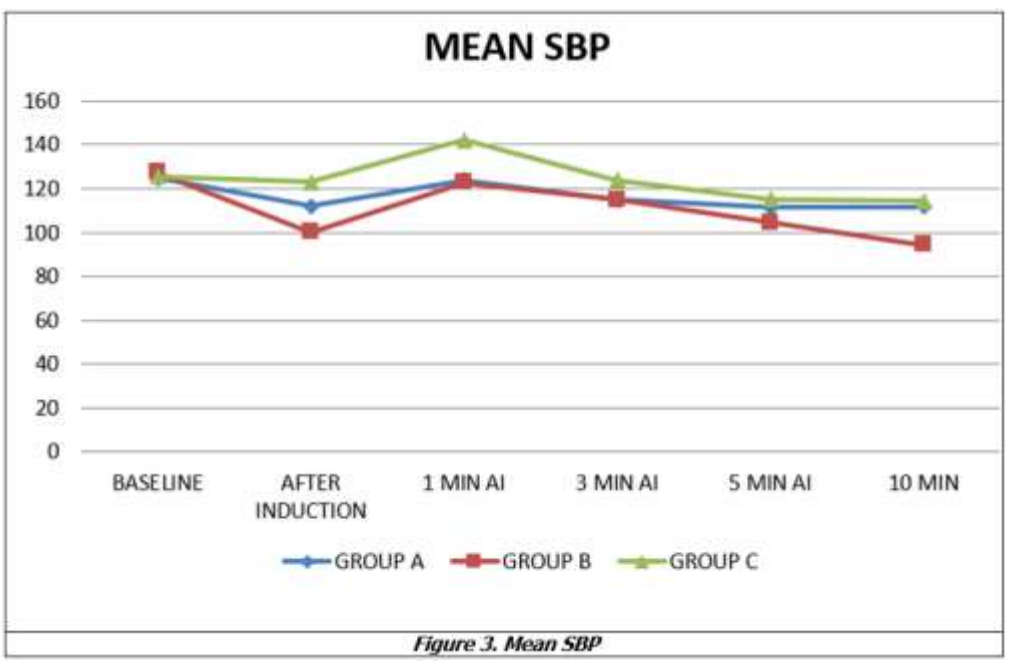

Figure 3. Mean SBP

- **Diastolic Blood Pressure (DBP)**

  As shown in table 3 and figure 4 DBP was comparable at baseline in all three groups. Changes in DBP was statistically significant in premedicated group after induction, 1, 10 min after laryngoscopy and intubation in comparison to placebo group (p value<0.05). Between pregabalin and clonidine, clonidine caused a greater reduction in DBP in comparison to pregabalin group after induction, 1, 3, 5, 10 min after laryngoscopy and intubation which was statistically significant at 10 min (p value<0.001).

Groups (n=30)	Baseline	After induction	1 min AI	3 min AI	5 min AI	10 min AI
Group A	81.53±9.909	72.90±12.078	82.37±16.272	75.57±10.931	71.47±12.022	73.07±9.829
Group B	81.63±9.13	63.87±12.98	79.43±12.86	74.93±14.35	68.4±10.156	60.23±7.03
Group C	79.07±10.1	77.37±21.32	91.23±13.79	79.97±14.74	72.13±15.51	75.8±14.58
p Value	0.514	0.005	0.006	0.293	0.485	0.00
p Value b/w Group A & B	0.968	0.007	0.442	0.848	0.290	<0.001

Table 3. Mean DBP

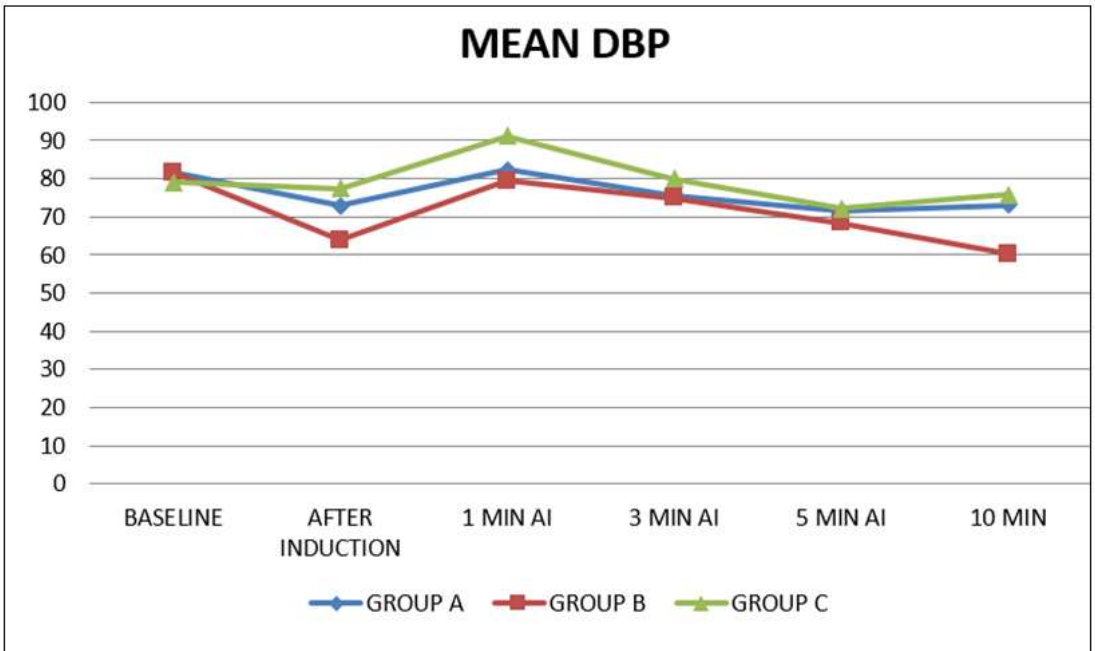

Figure 4. Mean DBP

- **Mean Blood Pressure (MBP)**
  As shown in table 4 and figure 5, MBP was comparable at baseline in the three groups. Changes in MBP were statistically significant in premedicated group after induction, 1, 10 min after laryngoscopy and intubation in comparison to placebo group (p value<0.05). Between clonidine and pregabalin, clonidine caused a greater reduction in DBP in comparison to pregabalin group after induction, 1, 3, 5, 10 min after laryngoscopy and intubation which was statistically significant at 10 min.

Groups (n=30)	Baseline	After Induction	1 min AI	3 min AI	5 min AI	10 min AI
Group A	93.20±12.680	83.33±13.494	95.67±18.041	85.87±13.325	82.50±13.114	83.93±10.027
Group B	94.20±9.550	74.37±13.255	90.80±15.751	87.40±14.771	79.53±11.113	71.10±7.563
Group C	92.13±11.066	89.83±22.820	106.07±16.569	92.30±16.009	84.77±17.310	86.93±14.858
p Value	0.774	0.003	0.002	0.216	0.357	0.00
p Value b/w Group A & B	0.731	0.012	0.270	0.674	0.348	<0.001

Table 4. Mean Blood Pressure

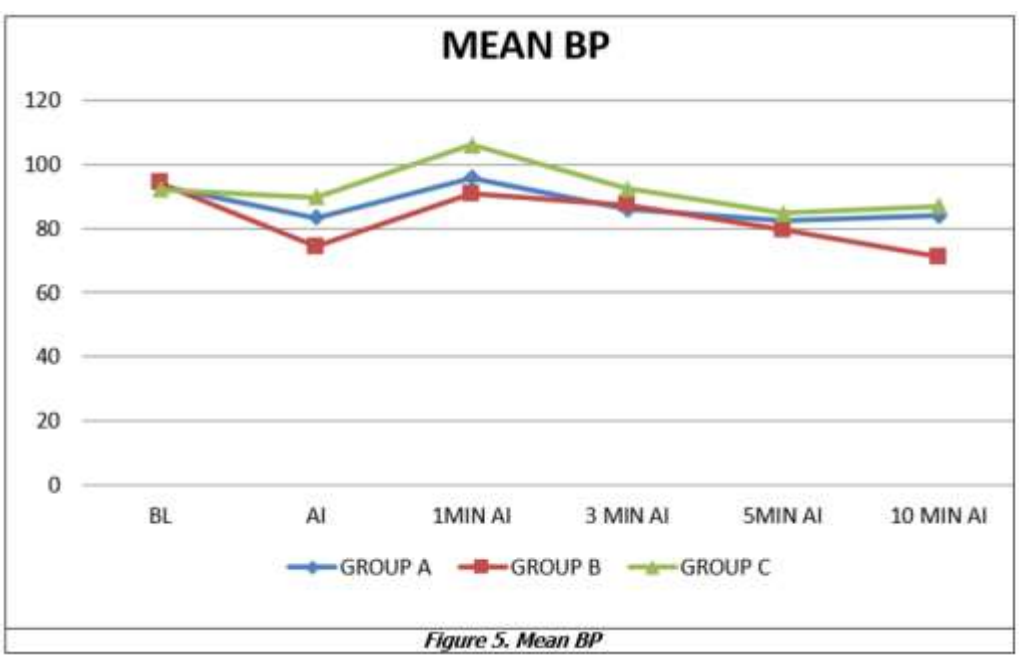

Figure 5. Mean BP

- Side Effect –In clonidine group, 1 patient had episode of hypotension in the intraoperative period, and responded to IV fluids, and 1 patient had episode of bradycardia and received in atropine 0.6 mg IV. These patients were excluded from the study and two other patients were recruited to make sample size 30.
- No other serious adverse effects were noted.

DISCUSSION

Demographic Profile

Demographic data like age, BMI (Body Mass Index), sex ratio were comparable in all the three groups (p value>0.05). The patients in the study were either ASA 1 or 2 with no significant history and were equally distributed between the groups.

Time Taken for Laryngoscopy and Duration of Surgery

As shown in figure 1 time taken for laryngoscopy was comparable in all three groups (group A-12.17, group B-11.93, group C-11.97 min), p value>0.05.

Time taken for laryngoscopy is similar to study done by singhal et al.[9]

(Group 1 clonidine-11.18, Group 2 gabapentin- 11.38 min).

Time taken for laryngoscopy is less than that in other similar studies by Gupta et al, Bhawana et al and khan et al.[10,11,12] Robert K Stoelting noted that the best way to prevent laryngoscopic reaction was to minimize the duration of laryngoscopy and intubation.[13] Hence in our study the duration of laryngoscopy was restricted as much as possible and all the laryngoscopies and intubations were performed by expert anaesthesiologist.

Heart Rate

As shown in table 1, figure 2, the mean heart rate at baseline, after induction, 1, 3, 5, 10 min after laryngoscopy and intubation was significantly lower in the clonidine group and pregabalin group in comparison to the control group (p value <0.05). Clonidine group caused a greater decrease in heart rate in comparison to the pregabalin group which was statistically significant after induction and 10 minutes following laryngoscopy and intubation. The attenuating effect of clonidine has also been described by Matot et al, Raval et al, Passi et al, Singh et al[14,15,16,17] Our findings are similar to study done by Gupta et al[10] and they concluded that oral premedication with clonidine and pregabalin have effective role in blunting hemodynamic response in comparison to control group and was statistically significant before induction, 1 min after intubation, 15 minutes after pneumoperitoneum, 30 minutes after pneumoperitoneum, after release of CO_2 and after extubation(p value <0.05). Clonidine caused greater attenuation of heart rate in comparison to pregabalin group. In another study by Singhal et al[9] concluded that heart rate in clonidine group remained below baseline at all times except at 1 min following intubation when transient rise of 5.33% was observed while gabapentin group shows that heart rate rise persisted until the end of study period and was statistically significant at all times compared with clonidine group. Although Singhal et al have used clonidine and gabapentin, the clonidine group shows better results in attenuating haemodynamic response just like in our study where clonidine fared better as far as decrease in heart rate is concerned. Khan et al[12] compared oral clonidine and pregabalin premedication and concluded from their study that clonidine was better than pregabalin and placebo group in blunting hemodynamic response. Mean heart rate at 1-minute interval after intubation was 88.7, 104.7, 103.5 in clonidine, pregabalin and placebo group respectively, p value <0.001. it seems there was no significant difference between pregabalin and placebo because of decreased dose of pregabalin used in their study.

Mean Blood Pressure

As shown in table 4 and figure 5, the mean blood pressure at baseline was comparable in all the three groups (p value>0.05). The mean blood pressure was lower in pregabalin and clonidine group in comparison to the control group and was statistically significant after induction, 1, 10 minutes after laryngoscopy and intubation (p value<0.05). Clonidine group caused a greater reduction in mean blood pressure in comparison to the pregabalin group and was statistically significant after induction and 10 minutes following laryngoscopy and intubation. Our study therefore shows that oral premedication with clonidine and pregabalin was superior to control group for attenuating the haemodynamic response (heart rate and blood pressure) to laryngoscopy and intubation and further to that clonidine was superior to pregabalin for attenuating the hemodynamic response.

Following studies also show a similar trend in attenuating mean arterial pressure similar to our study.

Gupta et al[10] in 2011 reported a similar observation when they compared the efficacy of oral premedication with pregabalin 150 mg versus clonidine 200 µcg for haemodynamic stability during laryngoscopy and pneumoperitoneum in laparoscopic cholecystectomy. After laryngoscopy, the attenuation of mean arterial blood pressure in the premedicated group was statistically significant as compared with the control group (p value <0.05).The attenuating effect of clonidine has also been described by Matot et al, Raval et al, Passi et al, Singh et al.[14,15,16,17] Bhawana et al[11] compared oral pregabalin 75mg, 150 mg and placebo, and no significant difference was observed in the MAP before and after premedication, but after laryngoscopy and intubation, the attenuation of MAP in the premedicated group was statistically significant and there was dose related decrease in mean arterial pressure when 75 mg pregabalin was compared to 150 mg of pregabalin. Singhal et al[9] concluded that MAP was attenuated more in clonidine group & it remained below baseline throughout the study period. In gabapentin group also, a fall in MAP was observed at all times except 1-minute following intubation when rise in MAP (7.55%) was observed

(p value<0.001), when compared with clonidine group. Khan et al[12] compared oral premedication with pregabalin 75 mg versus clonidine 300 µcg in attenuation of haemodynamic response following laparoscopy and endotracheal intubation. They observed that oral clonidine was superior to pregabalin and placebo in attenuating haemodynamic stress response to laryngoscopy and endotracheal intubation, but they did not observe any significant difference between pregabalin and placebo groups. The difference in the heart rate and blood pressure response between pregabalin and control group in our study in comparison to the above study may be attributed to the higher dose of pregabalin 150 mg used in our study.

CONCLUSION

In the present study, oral premedication with either pregabalin 150 mg or clonidine 200 mcg attenuates the haemodynamic response to laryngoscopy and intubation in comparison to control group. Clonidine is better than pregabalin for attenuation of stress response.

Based on our study, we strongly recommend oral pregabalin 150 mg and clonidine 200 mcg as premedicant. We recommend that larger study should be carried out in future in order to substantiate the current findings and beneficial effects of pregabalin and clonidine.

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