Original Research Article

Indian Journal of Anesthesia and Analgesia
November – December 2020;7(6)
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.7620.68

Comparative Study of Oral Clonidine, IV Fentanyl and IV Butorphanol in Attenuation of Hemodynamic Stress Response to Laryngoscopy and Endotracheal Intubation

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How to cite this article:

Sorathiya Prashant C, Rashmi D Souza. Comparative Study of Oral Clonidine, IV Fentanyl and IV Butorphanol in Attenuation of Hemodynamic Stress Response to Laryngoscopy and Endotracheal Intubation. Indian J Anesth Analg. 2020;7(6):1343–1349.

Abstract

Introduction: Laryngoscopy and endotracheal intubation is invariably associated with haemodynamic stress response which may have severe consequences in patients with comorbidities. Various drugs have been tried to attenuate this response. Ease of use, cost effectiveness and minimal side effects are some important considerations while choosing an agent. In this study we have compared the efficacy of oral clonidine with IV fentanyl and IV butorphanol in attenuating the stress response to laryngoscopy and intubation.

Materials and Methods: This is a prospective, randomised, comparative study carried out on 75 patients aged 20–60 years, ASA I/II physical status, scheduled for elective surgery. These patients were randomly allocated into three groups- GROUP A received IV Fentanyl 2mcg/kg and GROUP B received IV Butorphanol 40 mcg/kg five mins prior to induction respectively. GROUP C received Oral Clonidine 4 mcg/kg 90 mins prior to induction. All thepatients were assessed for heart rate, systolic blood pressure and diastolic blood pressure before induction, during laryngoscopy, after intubation at 1 min, 2 min, 3 min and 5 minrespectively.

Statistical analysis: The data was compared and analysed using Kruskal-Wallis test.

Results: There was an increase in the hemodynamic parameters post laryngoscopy and intubation in all the groups.Astatistically significant difference in the mean heart rate, systolic blood pressure and diastolic blood pressure was observed; the increase being significantly lower and short-lived in the oral clonidine group compared to the other two groups. Although all the three drugs were effective in attenuating the pressor response, oral clonidine was moreeffective and consistent compared to IV fentanyl and IV butorphanol.

Conclusion: Oral clonidine 4mcg/kg given 90 mins prior to induction is more effective than IV fentanyl and IV butorphanol in blunting the hemodynamic response to direct laryngoscopy and intubation without causing any significant side effects.

Keywords: Hemodynamic response; Oral clonidine; Fentanyl; Butorphanol.

Introduction

Direct laryngoscopy and endotracheal intubation is an integral part of general anesthesia. It is invariably associated withcardiovascular response such as, hypertension, tachycardia and at times arrhythmias, due to reflex sympathetic stimulation. While these changes are transient and probably of little consequence in healthy individuals, they may be detrimental in patients with hypertension, coronary artery disease and cerebrovascular diseases.

To overcome these undesirable effects, many strategies have been tried. These include deepening the plane of anesthesia, pre treatment with vasodilators, adrenoreceptor blockers, calcium channel blockers, lidocaine, opioids etc. However no single technique has been found to be entirely successful. An ideal agent should attenuate the pressor response, be easy to administer, economical, cause minimal side effects and not affect recovery from anesthesia.

Opioidsbind to specific receptors located in the cardiovascular regulatory centers, the sympathetic nervous system, and the vagal nuclei. This enables them to attenuate the pressor response to laryngoscopy and intubation. They are also commonly used in the perioperative period for analgesia, sedation and post-operative shivering.

Fentanyl,a synthetic opioid, is a pure agonist which has a rapid onset and short duration of action. It is a potent analgesic, cardio stable and isused widely to attenuate the pressor response to laryngoscopy and intubation.

Butorphanol, is an agonist-antagonist synthetic opioid, provides analgesia, sedation and is also used to attenuate pressor responses.

Clonidine is an imidazole derivative, α-2 adrenergic agonist with a central sympatholytic effect. It decreases the heart rate and causes a dose dependent decrease in systolic and diastolic blood pressure. It is well absorbed after oral administration with nearly 80% bio availability. Oral route is easy to administer and cost effective. Thus, it can be used as an effective alternative to attenuate the pressor response to laryngoscopy and intubation.

The present study was designed to compare the efficacy of Oral Clonidine with equipotent doses of IV Fentanyl and IV Butorphanol in attenuating the pressor response to direct laryngoscopy and endotracheal intubation.

Materials and Methods

This prospective randomised study was carried out on 75 patients, after obtaining a written informed consent, in a tertiary referral hospital. The study population consisted of patients aged 20–60 years, of either sex, belonging to ASAI/ II physical status, scheduled for elective surgeries under general anaesthesia.

Patients with ASA III/ IV physical status, age <20yrs and>60 years, with history of drug dependence, undergoing emergency procedures, having anticipated difficult airway, requiring more than one attempt or more than 30 secs for intubation were excluded from the study.

The study population was randomly allocated to three groups of 25 each. Group A received injection Fentanyl 2mcg/kg IV 5 minutes before induction, group B received injection Butorphanol 40mcg/kg IV 5 minutes before induction, group C received oral Clonidine 4mcg/kg (maximum of 200 mcg) 90 minutes before induction. Randomization was done using sealed envelope method.

A detailed history, thorough clinical examination and a written informed consent was taken a day prior to the surgery. Routine investigations including CBC, random blood sugar, ECG was done.

On arrival in the operating room, under standard monitoring (ECG, Non Invasive blood pressure, SpO_2 and Capnography), baseline parameters were noted and Inj. Glycopyrrolate 4mcg/kg IV, Inj. Ondansetron 0.15mg/kg IV given as routine premedication. After pre-oxygenation with 100% O_2 for 3minutes, general anaesthesia was induced with Inj. Thiopentone Sodium 2.5% 5mg/kg IV followed by Inj. Vecuronium 0.1mg/kg IV. Direct laryngoscopy and endotracheal intubation was done 3 mins later by a resident with more than one year of experience in anaesthesiology.

Anaesthesia was maintained using 0.8 to 1 MAC of Isoflurane in O_2 (50%) and N_2O(50%) mixture, with Inj. Vecuronium as the relaxant. Patients were mechanically ventilated with a tidal volume of 8–10ml/kg and a respiratory rate of 12/min.

The heart rate through continuous ECG monitoring, systolic blood pressure and diastolic blood pressure through NIBP were recorded by a single observeron arrival to the operating room (baseline values): pre-induction (i.e. 90 min after oral Clonidine in group C and 5 min after IV Fentanyl/ Butorphanol in group A and B respectively): during laryngoscopy: atintubation and at one, two, three and five minutes after intubation in all the

groups. No surgical stimulus was allowed during this period.

Hemodynamic response was defined as >25% increase in the value of hemodynamic parameters from thebaseline to 2 minutes after intubation.

On completion of surgery, neuro-muscular blockade was reversed with IV Neostigmine 0.05 mg/kg and IV Glycopyrrolate 8 mcg/kg. Patients were extubated once the appropriate criteria were met. Vitals- ECG, NIBP, SPO_2were monitored for an hour in the recovery room. Any postoperative complications including nausea, vomiting, sedation etc. were noted.

Statistical Analysis

The data at each of the measurement was presented as Mean ± SD. Since normality assumption was not followed, non-parametric tests were applied. To test the efficiency of each drug, the intra-group hemodynamic parameters were analysed using the Wilcoxon Signed Ranks test. The demographic profile and inter-group hemodynamic parameters were compared using the Kruskal-Wallis test. P value of < 0.05 was considered as significant.

Results

This study was carried out in 75 patients divided into three groups of twenty-five each. The demographic data is as shown in Table 1. The data in all the three groups were comparable with respect to age, sex distribution and weight (p >0.05).

1. *Heart Rate:* The Heart rate at various time intervals in the three groups is as shown in Table 2. The baseline heart rate was comparable in all the groups. It was observed that heart rate increased in all groups after intubation. However, the increase was less than 25% of the baseline values in the oral clonidine group. The increase was significantly less in oral clonidine group as compared to fentanyl group and butorphanol group at all times of the assessment i.e. during laryngoscopy, after intubation and at 1, 2, 3 and 5 minutes after intubation. At 5 minutes after intubation, the heart rate returned to the baseline value only in the oral clonidine group and remained elevated in the fentanyl and butorphanol group.(Fig. 1)

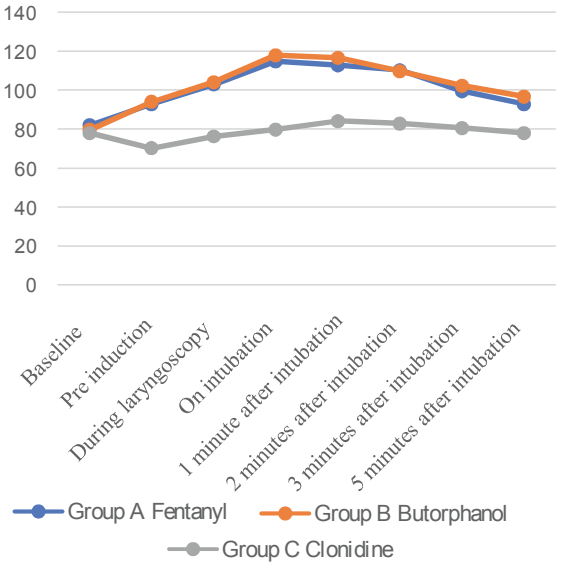

Fig. 1: Heart rate in all groups at various time interval.

Table 1: Demographic data

	Age (in years) Mean + SD	Number of patients		Weight (kgs) Mean + SD
		Males	Females	
Group A Fentanyl	38.40±10.42	13	12	56.00±6.19
Group B Butorphanol	35.92±11.16	11	14	57.96±5.96
Group C Clonidine	35.28±10.51	12	13	56.04±6.16
P-value	>0.05	>0.05	>0.05	>0.05

Table 2: Changes in heart rate.

Time Intervals	Group A Fentanyl Mean ± SD	Group B Butorphanol Mean ± SD	Group C Clonidine Mean ± SD	P-value
Baseline	82.08±10.33	79.73±10.10	78.08±9.39	0.112
Pre induction	92.92±8.33	94.04±13.41	70.24±7.40	<0.001
During laryngoscopy	103.08±10.40	104.12±14.32	76.32±8.10	<0.001
On intubation	114.92±10.91	118.00±13.71	79.8±8.72	<0.001
1 min after intubation	112.92±11.17	116.60±12.36	84.2±8.37	<0.001
2 mins after intubation	110.32±11.33	109.80±12.85	82.92±8.59	<0.001
3 mins after intubation	99.60±7.03	102.44±13.19	80.56±8.56	<0.001
5 mins after intubation	92.92±8.18	96.72±12.79	78.0±7.31	<0.001

# p<0.001 highly significant

2. *Systolic Blood Pressure:* The Systolic blood pressure at various time intervals in the three groups is as shown in Table 3. The baseline systolic blood pressure was comparable in all the groups. It increased in all groups after laryngoscopy and intubation. The extent of increase was less than 25% of the baseline values in all the groups. However, the increase was significantly less in oral clonidine group as compared to fentanyl group and butorphanol group at all times of the assessment i.e. during laryngoscopy, after intubation and at 1, 2, 3 and 5 minutes after intubation. The systolic blood pressure returned to the baseline value at 2 minutes after laryngoscopy and intubation in the oral clonidine group compared to 5 minutes after intubation in the fentanyl and butorphanol group.(Fig. 2)

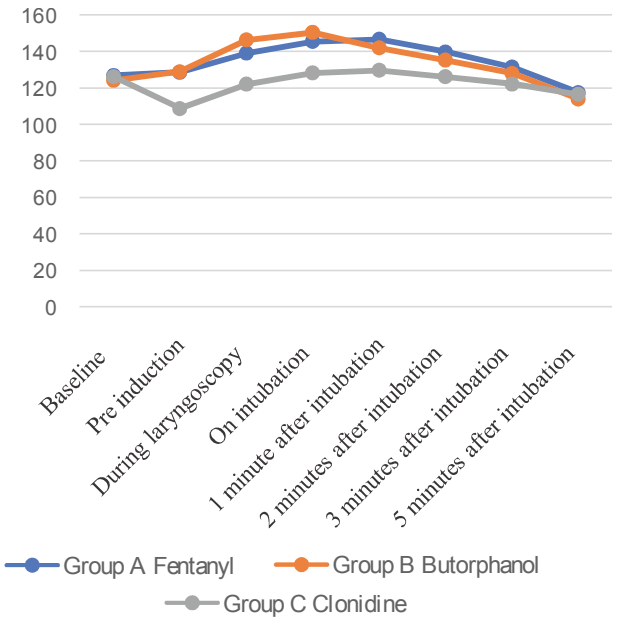

Fig. 2: Systolic blood pressure in all groups at various time interval.

3. *Diastolic Blood Pressure:* The diastolic blood pressure at various time intervals in the three groups is as shown in Table 4. The baseline diastolic blood pressure was not comparablein the three groups. The diastolic blood pressure increased in all groups after laryngoscopy and intubation. The extent of increase was less than 25% of the baseline values in all the groups. However, the increase was significantly less in oral clonidine group as compared to fentanyl group and butorphanol group during laryngoscopy, after intubation and at 1, 3 and 5 minutes after intubation. The diastolic blood pressure returned to the baseline value at 2 minutes after laryngoscopy and intubation in the oral clonidine group compared to 5 minutes after intubation in the butorphanol group. The diastolic blood pressure remained elevated above the baseline values in the fentanyl group. (Fig. 3).

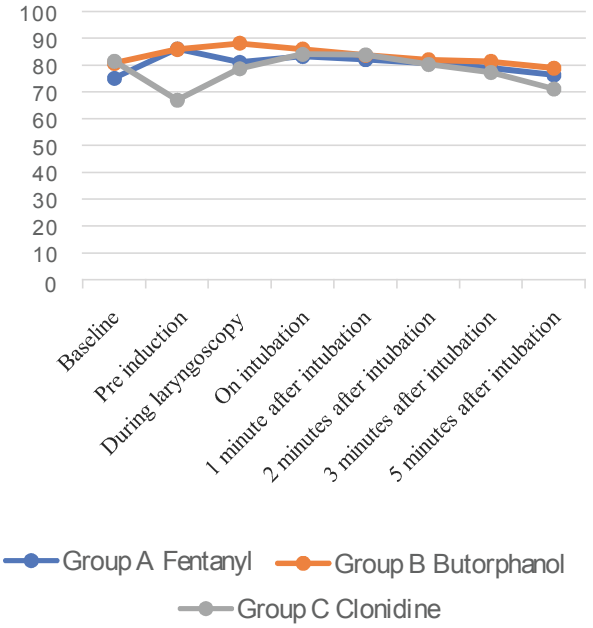

Fig. 3: Diastolic blood pressure in all groups at various time

Table 3: Changes in systolic blood pressure.

Time Intervals	Group A Fentanyl Mean ± SD	Group B Butorphanol Mean ± SD	Group C Clonidine Mean ± SD	P-value
Baseline	127.04±11.46	124.24±4.81	126.33±4.58	0.175
Pre induction	128.72±9.34	129.00±5.86	108.80±2.95	<0.001
During laryngoscopy	139.04±9.42	146.48±7.38	122.06±5.59	<0.001
On intubation	145.60±8.30	150.52±7.07	128.40±4.01	<0.001
1 min after intubation	146.72±7.97	142.16±6.66	129.73±4.89	<0.001
2 mins after intubation	139.84±7.81	135.28±7.04	126.13±4.75	<0.001
3 mins after intubation	131.44±7.73	128.20±7.02	122.26±4.35	<0.001
5 mins after intubation	117.60±4.92	114.16±7.20	116.60±3.60	0.022

# p<0.001 highly significant ## p<0.05 significant

Table 4: Changes in diastolic blood pressure.

Time Intervals	Group A Fentanyl Mean ± SD	Group B Butorphanol Mean ± SD	Group C Clonidine Mean ± SD	P-value
Baseline	75.20±3.87	80.68±3.75	81.46±4.13	<0.001
Pre induction	86.12±4.41	85.92±3.26	67.00±4.22	<0.001
During laryngoscopy	81.12±3.84	88.16±5.36	78.80±5.16	<0.001
On intubation	83.32±3.80	85.96±4.22	84.13±3.96	0.048
1 min after intubation	82.12±3.00	83.72±3.28	84.00±3.96	0.044
2 mins after intubation	80.72±2.67	81.96±4.42	80.33±3.96	0.447
3 mins after intubation	79.04±1.93	81.40±3.44	77.40±4.61	0.002
5 mins after intubation	76.44±1.73	78.96±3.57	71.20±3.38	<0.001

# p<0.001 highly significant## p<0.05 significant

Table 5: Postoperative complications.

	Group A Fentanyl	Group B Butorphanol	Group C Clonidine
Bradycardia	1	0	2
Nausea / Vomiting	1	3	0
Sedation	0	2	6

interval.

All the groups showed attenuation of the systolic and diastolic blood pressure after laryngoscopy and intubation with the values returning to baseline levels within 5 minutes after intubation. However, only oral clonidine group showed significant attenuation of the heart rate with values returning to the baseline at 5 minutes after intubation.

4. *Side Effects and Complications:* The side effects observed post operatively are as shown in table 5.

   The incidence of bradycardia was 4% in the fentanyl group and 8% in the clonidine group. It was transient and resolved without any treatment.

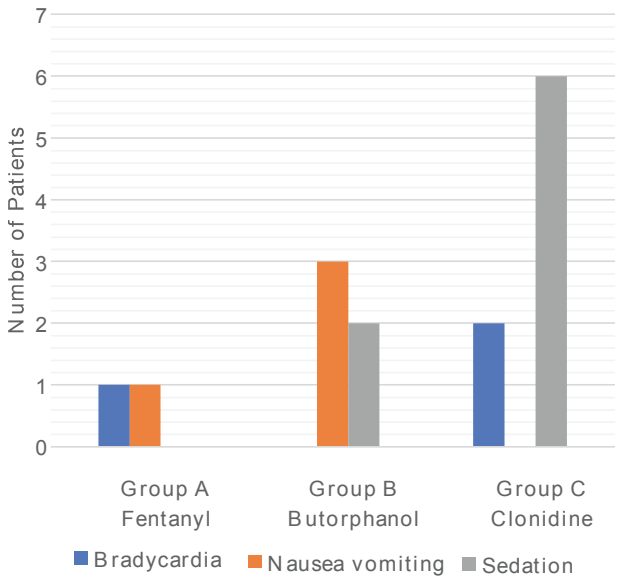

Fig. 4: Postoperative complications.

The incidence of nausea and vomiting was 4% in fentanyl group and 12% in butorphanol group post operatively and was treated with inj.ondansetron 4 mg IV.

The incidence of sedation was 8% in the butorphanol group and 24% in the oral clonidine group. However, all these patients were easily arousable upon verbal command and required no other intervention.

There were no intra operative complications seen.

Discussion

Induction of general anaesthesia, direct laryngoscopy and endotracheal intubation are known to produce marked cardiovascular changes due to reflex autonomic activity.[1] Studies have shown an average increase in blood pressure of 40%–50% and heart rate of 20%.[2] This response may be particularly hazardous for patients with cardiovascular and cerebrovascular diseases.[3]

Numerous attempts have been made to obtund these effects by various techniques like increasing adequate depth of anesthesia, minimising the duration of laryngoscopy, concomittant use of drugs likeopioids, benzodiazepines, lignocaine, adrenergic blockers, calcium channel blockers etc.[4] Although these stratergies did obtund the response to some extent, they failed to fulfil the desired criteria for complete attenuation.[5]

Fentanyl and Butorphanol are commonly used opioids for analgesic effects, sedation and also to attenuate the hemodynamic response to layngocopy and intubation.

Clonidine, an α2 agonist mainly used as an antihypertensive agent, is now being increasingly used as a premedicant as it provides attenuation of hemodynamic responses to intubation in addition to sedation, anxiolysis and decrease in the anaesthetic requirement, while maintaining normal baroreceptor responses.[6]

In our study, we have compared oral clonidine with IV fentanyl and IV butorphanol for attenuationof haemodynamic stress response to direct laryngoscopy and intubation.

Kautto UM et al[7] studied the effect of IV fentanyl in two different doses of 2 mcg/kg and 6 mcg/kg for attenuation of stress response. He concluded that the hemodynamic responses were effectively controlled in the fentanyl 2 mcg/kg group as well with minimal side effects.Therefore, we selected the dose of IV Fentanyl 2 mcg/kg in our study.

Pandit et al[8] in their comparative study of Butorphanol 40 mcg/kg and Fentanyl 2 mcg/kg for outpatient anaesthesia observed that unlike butorphanol, the post-intubation arterial pressure and heart rate in the fentanyl group were significantly higher than the base line values.In order to facilitate an effective comparison with IV Fentanyl 2mcg/kg, we selected an equipotent dose of IV Butorphanol 40 mcg/kg in our study.

Carabine UA et al[9] studied the effect of oral clonidine in doses of 0.1 mg, 0.2 mg and 0.3 mg as a premedicant. They concluded that 0.2 mg oral clonidineproduces significant reduction in anxiety, better quality of induction than 0.1mg and doses of 0.3mg caused significant hypotension persisting to the post operative period. Kulka Peter J et al[10] observed that the effects of clonidine on sedation and haemodynamic variables are dose related and increasing the dose to more than 4 mcg/kg does not further enhance efficacy. Therefore we selected the dose of oral clonidine 4 mcg/kg in our study.

In 2002, Rawal DL et al[5] studied oral clonidine as a premedicant for the attenuation of hemodynamic response to laryngoscopy and intubation.Oral clonidine 4mcg/kg was compared with oral diazepam 0.2mg/kg, both given 90 minutes prior to induction and hemodynamic parameters noted for every minute upto 5 mins after intubation.They observed that oral clonidine caused significant reduction in heart rate, systolic and diastolic blood pressure with values returning to baseline within 5 minutes of intubation. It also produced significant anxiolysis and lesser sedation compared to diazepam. No adverse effects were observed.

In 2011,Singh et al[11] studied the effect of oral clonidine premedication on perioperative hemodynamic response in patients undergoing laparoscopic cholecystectomy. They observed a significant reduction in heart rate, systolic and diastolic blood pressure at 1minute and 5 minutes after intubation, with values remaining significantly lower than the control group throughout the perioperative period. They also noted significant reduction in intra operative anaesthetic and post operative analgesic requirements. There was no significant difference in the side effects observed in both the groups.

In 2019, Rukmini G et al[12] compared oral clonidine and IV fentanyl in attenuation of hemodynamic responses to laryngoscopy and intubation. The heart rate, systolic and diastolic blood pressure was significantly higher in the fentanyl group upto three minutes after intubation. The hemodynamic parameters were comparable at five minutes after intubation. These findings are similar to the findings in our study.

In 2017, Anand S et al[13] performed a study on comparison of two opioids, IV Fentanyl with IV Butorphanol in propofol based anesthesia to attenuate the hemodynamic response. They concluded that although both the drugs were effective in attenuating the increase in heart rate, systolic and diastolic blood pressure, IV Fentanyl was far more superior than IV Butorphanol to attain hemodynamic stability. A similar finding was also observed in our study.

In our study we observed that although all the three drugs did aid in attenuation of pressor response to laryngoscopy and intubation in varying extent, Oral Clonidine 4mcg/kg was stastically more significant, with the hemodynamic parameters- heart rate, systolic and diastolic blood pressure returning to baseline values within 3 mins of endotracheal intubation. On comparing IV Fentanyl 2mcg/kg and IV butorphanol 40mcg/kg using descriptive stastistics (Co-efficient of variation), IV Fentanyl was more consistent in attenuating hemodynamic response to laryngoscopy and intubation than Butorphanol.

Conclusion

In our study, we conclude that Oral Clonidine 4mcg/kg given as a pre-medicant is more effective in attenuating the haemodynamic stress response to direct laryngoscopy and endotracheal intubation as compared to IV Fentanyl 2mcg/kg and IV Butorphanol 40mcg/kg. The ease of administration, cost effectiveness, anxiolysis and peri-operative

hemodynamic stability it offers, projects it as a safe and useful alternative.

Financial support and sponsorship: Nil

Conflict of interest: None declared

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