Comparison of Haemodynamic responses of clonidine and higher dose of Nalbuphine during laryngoscopy and endotracheal intubation in laparoscopic cholecystectomy operation: an observational study

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Abstract:

Background: Laryngoscopy and tracheal intubation are essential for patients undergoing surgery under general anaesthesia, which invariably is associated with certain cardiovascular changes such as tachycardia, rise in blood pressure and a wide variety of cardiac arrhythmias. The study was conducted to compare the effect of intravenous nalbuphine (0.4mg/kg) and clonidine (2μg/kg) during laryngoscopy and intubation on haemodynamic responses**. Methods:** The present hospital based observational study was conducted in the Burdwan Medical College and Hospital, Burdwan, West Bengal, India between February 2021 and August 2022. Patients who was admitted for laparoscopic cholecystectomy in department of General Surgery who was scheduled forsurgery fulfiilling the requisite criteria. Statistical data were analysed by using Microsoft Excel and SPSS V.20 software. **Results:** The study included 22 patients in each group. The mean age of the patients ofgroup C was 35.59±9.220 years and the mean age of the patients of group Nwas38.18±9.674years. The mean duration of surgery in the patients of group C was 85.82±4.837 minutes and the mean duration of surgery in the patients of group N was 84.09±4.363 minutes. The heart rates in both groups started reducing from the baseline as the anesthesia progressed. The systolic blood pressure in both groups started reducing from the baseline as the anesthesia progressed. The diastolic blood pressure in both groups started reducing from the baseline as the anesthesia progressed. The SPO2 in group N started slightly reducing from the baseline as the anesthesia progressed and came to normal. The respiratory rates in both groups started reducing from the baseline as the anesthesia progressed and came to normal. **Conclusion:** Clonidine (2 μg/kg) was more effective in reducing the hemodynamic changes of laryngoscopy and intubation than nalbuphine (0.4mg/kg), when administered as premedication before induction.

Keywords: Haemodynamic responses, clonidine, Nalbuphine, laryngoscopy, cholecystectomy

Introduction:

The hemodynamic response to laryngoscopy and tracheal intubation does not present a problem for most patients. However, a subgroup of patients, which includes those with coronary artery disease, recent myocardial infarction, hypertension, pre-eclampsia, and cerebrovascular pathology such as tumours, a neurysmsor increased intracranial pressure, are at increased risk of morbidity and mortality. The therapeutic armamentarium to counter act the cardiovascular responses to laryngoscopy and tracheal intubation includes a wide variety of drugs, techniques and routes of administration.[1]

The increase in pulse rate and blood pressure are frequently transitory, variable and unpredictable.[2]

The hemodynamic response is important especially in patients undergoing laparoscopic surgeries because of the physiological changes caused by pneumoperitoneum created by CO2 insufflation.[2] Various drugs and induction agents have been tried to prevent hemodynamic response of laryngoscopy.

These drugs include Thiopentone, Propofol, Esmolol, Lignocaine, Magnesium, Vasodilators and Opioids etc. Each of these mentioned drugs has its own limitations.[3-10]

Cholecystectomy was considered the surgical procedure for gall stone disease (cholelithiasis). Laparoscopic cholecystectomy (LC) is considered the gold standard treatment for most of the gall bladder diseases. The advantages of LC are earlier return of bowel function, less post-operative pain, cosmetic, shorter duration of hospital stay and also earlier return to full activity.

Anide alanaesthetic drugs or technique should have a rapid onset of action, be safe and convenient to prepare and administer, besides minimizing the hemodynamic changes. It must be applicable to patients of all age groups, prevent impairment of cerebral blood flow and avoid awareness during anesthesia. It should not also affect the duration of anaesthesia and recovery characteristics.

Clonidine, partial α2 adrenergic agonist, decreases the sympathetic nervous system outflow from central nervous system to peripheral tissues and inhibit release of norepinephrine. It has sedative, analgesic and antihypertensive action in addition to reduction of the anaesthetic drugs requirement.[11,12]

Nalbuphine is a semi-synthetic agonist-antagonist opioid analgesic. It is a gonist at kappa (κ) receptors and acts as antagonist at mu (μ) receptors. Nalbuphine not only suppresses the hemodynamic response but also provide intraoperative hemo dynamic stability with prolonged duration of analgesia. Its potential safety in over dosage i.e. ceiling effect in respiratory depression, makes nalbuphine an ideal analgesic during anaesthesia.[13-15]

Therefore, it was decided that an observational study was to bedone between the higher dose of nalbuphine and usual dose of clonidine to determine the better intravenous analgesic agent to attenuate the haemodynamic response during laryngoscopy and endotracheal intubation in laparoscopic cholecystectomy surgery.

Materials and Methods:

This hospital based observational study was conducted in the Burdwan Medical College and Hospital. Patients who was admitted for laparoscopic cholecystectomy in department of General Surgery who was scheduled for surgery fulfilling the requisite criteria. The duration of the study was 18 months from February 2021 to August 2022.

Inclusion criteria:

Patients fulfilling the criteria under American Society of Anaesthesiologists Grade 1 and 2,Mallampati Grade 1 and 2, Mouth opening>2 fingers, age 18-60 years, Male and Female patients and Body mass index<30kg/sq.ft.

Exclusion criteria:

Patients fulfilling the criteria under American Society of Anaesthesiologists Grade 3 and 4,Mallampati Grade 3 and 4, Recent sore throat, cough and cold, Mouth opening<2 fingers, Anticipated risk of aspiration.(not fasted or with a history of Gasto- oesophageal reflux disease), Bleeding disorder, Morbid Obesity, Uncomplicated diabetes mellitus and metabolic Disorder, Neurological illness, Uncompensated liver, heart and renal disease, Patients having uncontrolled bronchial asthma, C.O.P.D., or, any other respiratory disease.

Sample Size:

Assuming p value <0.05 to be significant and considering effect to be two sided, we got z alpha=1.96, assuming power of the study to be 90%, we get z 1-beta=1.28, considering an effect size(difference in heart rate after study drug) of 5.87 to be statistically significant, we got n>2[z α+z 1-β]2 multiplied by S.D.2/d2, we got n=22. Hence maximum 22 patients will be taken in each group.

Parameters Studied:

Heart rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure, SPO2, End Tidal carbon dioxide.

Laboratory Investigations:

The routine investigations required for determining the fitness of patients undergoing laparoscopic surgery under general anaesthesia according to institutional protocol.

Method of Data Collection:

Data were recorded in case record sheet. The changes in haemodynamic factors (pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, electrocardiogram, spo2, respiratory rate) at the time of intubation, 1 min after intubation, 3 mins after intubation, 5 mins after intubation, 10 mins after intubation, 15 mins after intubation was observed

Method of Data Analysis Plan:

Statistical Method:- Categorical variables were expressed as number of patients and percentage of patients and compared across 2 groups(Pearson's chi square chart test for independence of attributes/Fischer's exact test as appropriate).Continuous variables were expressed as Mean ± standard deviation and compared across 2 groups using unpaired t test if the data follows normal distribution and Mann-Whitney U test if the data does not follow the normal distribution. The statistical software SPSS VERSION 20 was used for the analysis. An alpha level of 5%had been taken that was if any p value is <0.05, it was considered as significant.

Ethical considerations:

Study was initiated after obtaining the informed consents from the participants and ethical clearance from the institutional ethical committee.

Results:

Table1. Comparison of demographic and clinical parameters

Parameters	Group	N	Mean	SD	Pvalue
Age(years)	C	22	38.59	9.220	0.887
	N	22	38.18	9.674	
Sex (%)	C	22	Male:10(45.5%), Female:12(54.5%)		0.273
	N	22	Male:13(59.1%), Female:9(40.9%)		
ASA(%)	C	22	ASAI:13(59.1%),ASAII:9 (40.9%)		0.273
	N	22	ASA I:10(45.5%),ASAII:12(54.5%)		
Height(cm)	C	22	161.91	3.558	0.935
	N	22	162.00	3.792	
Weight(kg)	C	22	63.45	4.426	0.574
	N	22	64.14	3.509	
Durationof surgery(min)	C	22	85.82	4.837	0.221
	N	22	84.09	4.363	

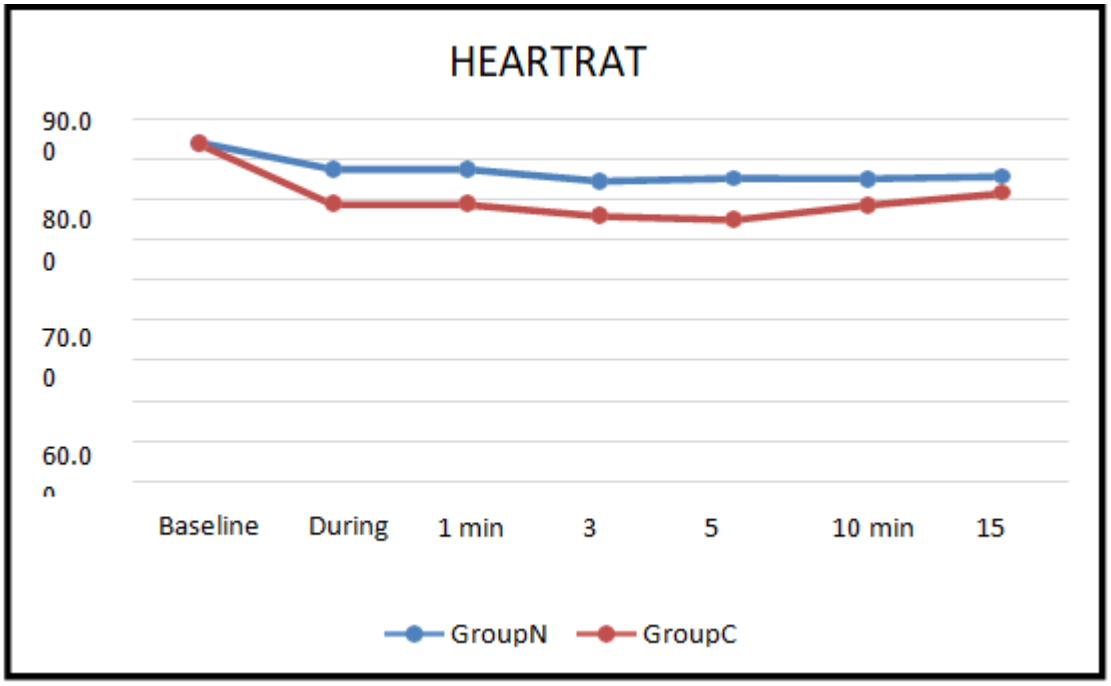
The study included 22 patients in each group. The mean age of the patients of group C was 35.59±9.220 years and the mean age of the patients of group N was 38.18±9.674years. In group C, there were 45.5% male and 54.5% female and in group N, there were 59.1% male and 40.9% female. In group C, there were 59.1% % patients with ASA I and 40.9% patients with ASA II and in group N, there were 45.5% % patients with ASA I and 54.5% patients with ASA II. The mean height of the patients of group C was 178.2±4.2 cm and the mean height of the patients of group N was 178.5±3.6 cm. The mean weight of the patients of group C was 68.8±3.0kg and the mean weight of the patients of group N was 67.2±2.8 kg. The mean duration of surgery in the patients of group C was 85.82±4.837 minutes and the mean duration of surgery in the patients of group N was 84.09±4.363 minutes. None of these differences were statistically significant. (Table 1)

Table2.Comparison of heart rate between the groups at different time intervals

Intervals	Group	N	Mean	SD	Pvalue
Baseline	C	22	83.59	9.287	0.871
	N	22	84.05	9.136	
During Intubation	C	22	70.95	7.520	0.001*
	N	22	77.41	8.851	
1 min	C	22	70.95	7.520	0.034*
	N	22	77.41	8.851	
3 min	C	22	68.08	7.253	0.022*
	N	22	74.41	9.127	
5 min	C	22	67.17	7.263	0.015*
	N	22	75.09	8.286	
10 min	C	22	70.8	7.641	0.000*
	N	22	75.05	8.392	
15 min	C	22	73.72	7.811	0.765
	N	22	75.55	8.210	

*Statistically significant difference exists ($p<0.05$)

Figure 1: Heart rate during the anesthesia



The heart rates in both groups started reducing from the baseline as the anesthesia progressed. The fall in heart rate was found more in group C than in group N. Statistically significant differences in heart rate between the groups were found during intubation,1,3,5 and10 minutes. (Table 2, figure 1)

Table3.Comparison SBP between the groups at different time intervals

Intervals	Group	N	Mean	SD	Pvalue
Baseline	C	22	125.82	6.084	0.666
	N	22	126.68	7.074	
During Intubation	C	22	117.45	5.490	0.018*
	N	22	123.91	7.037	
1 min	C	22	113.35	5.711	0.024*
	N	22	120.95	7.168	
3 min	C	22	111.49	5.537	0.005*
	N	22	119.27	6.584	
5 min	C	22	110.72	5.710	0.000*
	N	22	117.95	5.794	
10 min	C	22	112.75	3.922	0.031*
	N	22	116.91	7.164	

15 min	C	22	114.49	3.319	0.654
	N	22	116.27	6.258	

*Statistically significant difference exists(p<0.05)

The systolic blood pressure in both groups started reducing from the baseline as the anesthesia progressed. The fall in systolic blood pressure was found more in group C than in group N. Statistically significant differences in systolic blood pressure between the groups were found during intubation, 1, 3, 5 and 10 minutes. (Table 3)

Table4.Comparison DBP between the groups at different time intervals

Intervals	Group	N	Mean	SD	P value
Baseline	C	22	82.64	4.065	0.108
	N	22	85.36	6.651	
DuringIntubation	C	22	77.4	6.662	0.006*
	N	22	80.14	4.167	
1 min	C	22	74.54	6.657	0.000*
	N	22	77.41	4.171	
3 min	C	22	70.81	5.853	0.004*
	N	22	75.18	4.067	
5 min	C	22	68.99	5.306	0.020*
	N	22	73.18	3.948	
10 min	C	22	69.44	3.566	0.047*
	N	22	71.05	3.909	
15 min	C	22	70.13	2.506	0.471
	N	22	70.59	3.246	

*Statistically significant difference exists(p<0.05)

The diastolic blood pressure in both groups started reducing from the baseline as the anesthesia progressed. The fall in diastolic blood pressure was found more in group C than in group N. Statistically significant differences in diastolic blood pressure between the groups were found during intubation, 1, 3, 5 and 10 minutes. (Table 4)

Table5.Comparison MAP between the groups at different time intervals

Intervals	Group	N	Mean	SD	P value
Baseline	C	22	97.32	3.62	0.297

	N	22	98.85	5.75	
During Intubation	C	22	90.67	5.48	0.000*
	N	22	94.73	3.71	
1 min	C	22	87.48	5.70	0.001*
	N	22	91.93	3.84	
3 min	C	22	84.37	5.17	0.011*
	N	22	89.88	3.77	
5 min	C	22	82.9	4.88	0.029*
	N	22	88.11	3.53	
10 min	C	22	83.88	3.08	0.036*
	N	22	86.34	3.89	
15 min	C	22	84.92	2.32	0.795
	N	22	85.82	2.69	

*Statistically significant difference exists($p<0.05$)

The mean arterial pressure in both groups started reducing from the baseline as the anesthesia progressed. The fall in mean arterial pressure was found more in group C than in group N. Statistically significant differences in mean arterial pressure between the groups were found during intubation, 1, 3, 5 and 10 minutes. (Table 5)

Table6. Comparison SPO_2 between the groups at different time intervals

Intervals	Group	N	Mean	SD	Pvalue
Baseline	C	22	99.91	.294	0.467
	N	22	99.82	.501	
DuringIntubation	C	22	99.91	.294	0.032*
	N	22	94.22	.501	
1 min	C	22	99.95	.213	0.000*
	N	22	94.35	.213	
3 min	C	22	99.95	.213	0.041*
	N	22	94.35	.213	
5 min	C	22	100	0.000	0.002*

	N	22	94.35	.213	
10 min	C	22	99.95	.213	0.010*
	N	22	96.75	.213	
15 min	C	22	100	0.000	0.323
	N	22	98.85	0.213	

*Statistically significant difference exists(p<0.05)

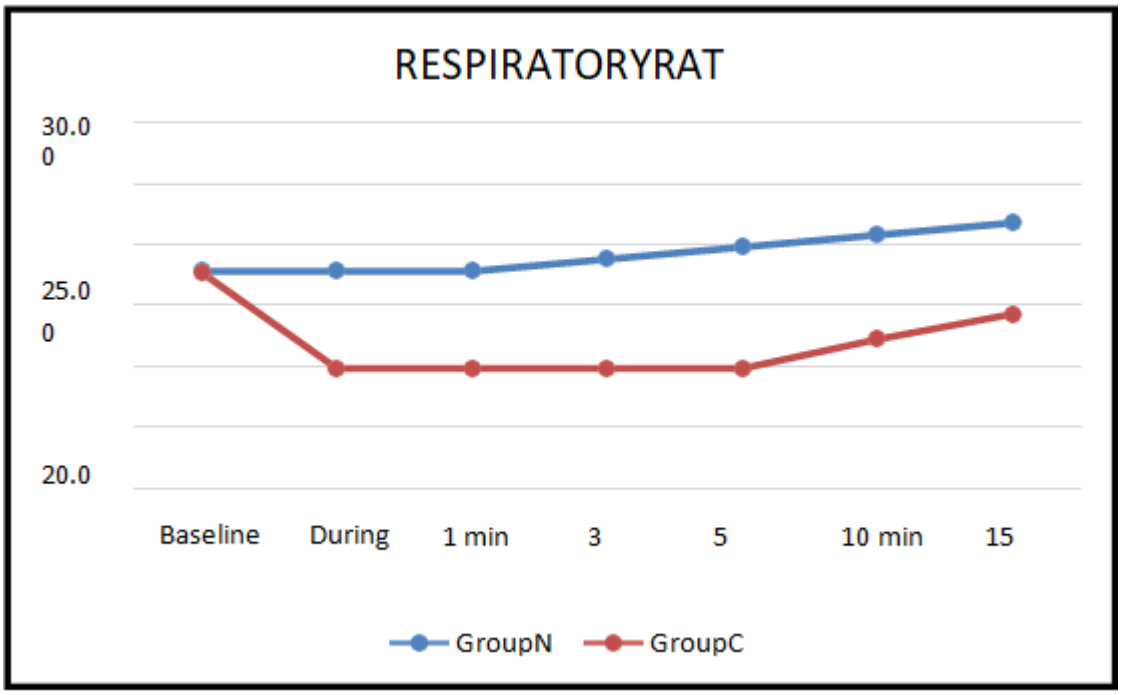
The SPO2 in group N started slightly reducing from the baseline as the anesthesia progressed and came to normal. The SPO2 in group C was stable throughout the intervals. Statistically significant differences in SPO2 between the groups were found during intubation, 1, 3, 5 and 10 minutes. (Table 6)

Table7. Comparison respiratory rate between the groups at different time intervals

Intervals	Group	N	Mean	SD	Pvalue
Baseline	C	22	17.73	1.42	0.836
	N	22	17.82	1.46	
During Intubation	C	22	12.13	1.42	0.003*
	N	22	17.82	1.46	
1 min	C	22	12.13	1.42	0.028*
	N	22	17.82	1.46	
3 min	C	22	12.13	1.42	0.001*
	N	22	18.82	1.46	
5 min	C	22	12.13	1.42	0.000*
	N	22	19.82	1.46	
10 min	C	22	14.53	1.42	0.044*
	N	22	20.82	1.46	
15 min	C	22	16.63	1.42	0.000*
	N	22	21.82	1.46	

*Statistically significant difference exists(p<0.05)

Figure 2: Respiratory rate between the groups at different time intervals



The respiratory rates in both groups started reducing from the baseline as the anesthesia progressed and came to normal. The fall in respiratory rate was found more in group C than in group N. Statistically significant differences in respiratory rate between the groups were found during intubation, 1, 3, 5, 10 and 15 minutes. (Table 7, Figure 2)

Discussion:

Direct laryngoscopy and intubation is most noxious stimuli during airway management due to intense sympathetic discharge and release of catecholamine, which manifested as hypertension and tachycardia. These short lived hemodynamic changes can be harmful in patients with preexisting myocardial disease or cerebral insufficiency. If no specific measures are taken to prevent these hemodynamic changes, the cardiac work load may be increased which in turn may terminate in perioperative myocardial ischemia or acute heart failure. Surgical stress also leads to increase catecholamine release which can further intensify the intraoperative hemodynamic instability. The therapeutic armamentarium to counteract the hemodynamic changes during laryngoscopy and intubation includes a wide variety of drugs, technique and route of administration.

Clonidine is alpha-2 agonists and showed pharmacological effects on blood pressure and heart rate, due to its sympathoinhibitory action. It has analgesic, sedative and anxiolytic profile.[7]Nalbuphine is an agonist-antagonist opioid analgesic causes less respiratory depression by activating the supraspinal and spinal kappa receptors. It does not allow increase in systemic blood pressure, pulmonary blood pressure, heart rate, thus may be useful for providing sedation and analgesia for cardiac patients.[8,9] The selection of dosages for the present study was based on the assumption that which almost equipotent doses could supress the hemodynamic changes with minimal side effects. For the present study, clonidine in dose of 2 µg/kg and nalbuphine in dose of 0.4mg/kg were selected for intravenous premedication

This study included 22 patients in each group. The mean age of the patients of group C was 35.59±9.220 years and the mean age of the patients of group N was 38.18±9.674 years. Mean weight of the patients of group C was 68.8±3.0 kg and the mean weight of the patients of group N was 67.2±2.8 kg. Salony Agarwal et al compared the efficacy of intravenous premedication of clonidine(2µg/kg) versus nalbuphine on intraoperative haemodynamic profile of patients during surgery under general anaesthesia. The

study mentioned mean age 47.62±10.4 for group A received clonidine (2 μg/kg) and 48.54±9.4 received nalbuphine (0.2 mg/kg) and mean weight 59.17± 7.5and60.83±9.3 for group A& B.[16]

In this study, the heart rates in both groups started reducing from the baseline as the anesthesia progressed. The fall in heart rate was found more in group C than in group N. Statistically significant differences in heart rate between the groups were found during intubation,1,3,5 and10 minutes.

The systolic blood pressure in both groups started reducing from the baseline as the anesthesia progressed. The diastolic blood pressure also in both groups started reducing from the baseline as the anesthesia progressed. The mean arterial pressure in both groups started reducing from the baseline as the anesthesia progressed. The SPO_2in group N started slightly reducing from the baseline as the anesthesia progressed and came to normal. The SPO_2in group C was stable throughout the intervals. The respiratory rate sin both groups started reducing from the baseline as the anesthesia progressed and came to normal.

Carabine UA et al, studied the effect of clonidine on the press or and heart rate response to tracheal intubation. They pre-treated the 30 patients with either clonidine 1.25 μg/kg, or clonidine 0.625 μg/kg or an equivalent volume of normal saline , given intravenously 15 minutes before induction of anaesthesia. They found the attenuation of pressor response to intubation inpatients of both clonidine groups with statistically significant difference among the group, which indicated that the lower dose of clonidine is alsoappropriate.[17]

Tripathi DC et al, observed the attenuated hemodynamic stress response to pneumoperitoneum, but not of intubation and extubation, when clonidine was given intravenously in the dose of 1μg/kg, while clonidine in dose of 2μg/kg, prevented the hemodynamic stress response to pneumoperitoneum along with that of intubation and extubation.[18]

Nalbuphine has been used in doses of and 0.3 mg/kg by Berg AA et al, topreventthemarkedriseinheartrateandbloodpressure duringlaryngoscopyand intubation.[19] Kothari D et al, have administered 0.2 mg/kg nalbuphine to attenuate the hemodynamic responses.[20]

Priti M Chawda et al studied the efficacy of nalbuphine in preventing the increase in heart rate and mean arterial pressure in response to laryngoscopy and intubation.[21] They observed significant rise in heart rate in the control group (20.4%) after intubation at 2 min when compared to nalbuphine group(16.66%). Heart rate and mean arterial pressure gradually decreased after 3 to8 min in control group but always remained higher than patient of nalbuphine group, thus concluded that nalbuphine attenuated the hemodynamic response to laryngoscopy and intubation. Similar results were found by Chaudhari M etal,showingincreaseinmeanheartrateandincreaseins ystolicbloodpressureinpatientsofnalbuphinegroupw hichwasstatisticallyhighlysignificant compared to clonidine group, immediately after intubation.[22] The increase in diastolic blood pressure and mean arterial pressure in nalbuphine group was statistically significant when compared to clonidine group immediately after intubation and then after at 1, 3, 5, 7, 10 min and 15 min after intubation. Nath R et al concluded in their study that nalbuphine (0.2mg/kg) produced stable hemodynamics during stressful period of laryngoscopy and intubation by virtue of its reduction in pulse rate, systolic blood pressure and diastolic blood pressure with fewer adverse effects and good analgesia[23]

BhaleraoPMetalobservedthatintraoperativemeanpul seratewas90.82±4.81 beats/min in control group while it was 74.76±9.88 beats/min in clonidine group. The mean systolic blood pressure was 137.87±4.89 and125.79±6.44 mmHg respectively.[24] They concluded that premedication with intravenous clonidine is effective method to provide stable hemodynamics and protection against stress response induced during laparoscopic cholecystectomy. Ray M, Bhattacharjee DP et al concluded in their study that immediately after laryngoscopy and intubation, heart rate increased by 10bpm in patients of clonidine group, while mean arterial pressure in clonidine group decreased significantly for all measurements with the exception during intubation and after induction.[25] Altan A et al studied clonidine in dose of3μg/kg and found that, mean arterial pressure increased by 16 mm Hg in control group, whereas in clonidine group, the mean arterial pressure increased only by10mm Hg, which showed clonidine has

significant blunting effectof pressor response of laryngoscopy and intubation[26] The present study also observed that clonidine effectively reduced the hemodynamic changes.

Similar results were found by Chaudhari MJ et al, showing increase in mean heart rate and mean blood pressure in patients of nalbuphine group which was statistically highly significant compared to clonidine group, immediately after intubation till 20 minutes.[22]

Zalunardo MP et al, compared the oral clonidine with intravenous clonidine 3µg /kg, and observed no increase of mean heart rate during endotracheal intubation in patients of intravenous clonidine group when compared with the placebo and the oralclonidinegroup.[27]

Altan A et al, studied clonidine in dose of 3 µg/kg and found that, mean arterial pressure increased only by 10 mmHg in patients of clonidine group while it increased by 16 mmHg in control group, which showed clonidine has significant blunting effect of pressor response of laryngoscopy and intubation.[26] Present study also states that clonidine effectively attenuated the hemodynamic pressor responses of laryngoscopy and surgery. The present study findings are in consistence with these previous clinical studies. Basedon the results of the present study and the above discussion, it can beconcludedthatclonidine0.2µg/kgwasmoreeffectiveinattenuatinghemodynamic pressor responses to laryngoscopy and intubation as well as surgical stress than nalbuphine 0.4mg/kg when administered intravenously as premedication.

Conclusions:

Based on the results of the present study and the it can be concluded that clonidine 0.2 µg/kg was more effective in attenuating hemodynamic pressor responses to laryngoscopy and intubation as well as surgical stress than nalbuphine 0.2 mg/kg when administered intravenously as premedication, 10 minutes before induction.

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Conflict of interest:

None declared

Ethical approval:

The study was approved by the institutional ethics committee

References:

1. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola K, Smith G. Plasma catecholamine responses to tracheal intubation. Br J Anaesth.1983; 55: 855–860.
2. Kautto UM. Attenuation of the circulatory response to laryngoscopy and intubation by Fentanyl. ActaAnaesthesiol Scand. 1982 Jun [cited 2019 Oct29];26(3):217–21.
3. Maguire AM, Kumar N, Parker JL, Rowbotham DJ, Thompson JP. Comparison of effects of remifentanil and alfentanil on cardiovascular response to trachealintubation in hypertensive patients. Br J Anaesth. 2001 Jan [cited 2019 Oct 29];86(1):90–3.
4. S M, Reddy P B, P Savdi V, K T R. A randomized controlled parallel study of Nalbuphine and Fentanyl on hemodynamic response to laryngoscopic and laparoscopic stress in patients undergoing laparoscopic appendectomy under general anaesthesia. Indian J ClinAnaesth. 2018 Dec 30;5(4):505–11.
5. Khan FA, Kamal RS. Effect of buprenorphine on the cardiovascular response to trachealintubation. Anaesthesia. 1989 ;May44(5):394–7.
6. Minai FN, Khan FA. A Comparison of Morphine and Nalbuphine for INTraoperative and Postoperative Analgesia. J Pak Med Assoc. 2003 Sep;53(9):391–6.
7. Chawda PM, Pareek MK, Wlehta KD. Effect of Nalbuphine on haemodynamic response to orotrachealintubation. J AnaesthesiolClinPharmacol. 2010;26(4):458–60.
8. Khan FA, Hameedullah. Comparison of Fentanyl and Nalbuphine in total INTravenousanaesthesia (TIVA). J Pak Med Assoc. 2002 Oct 1;52(10):459– 65.
9. Martineau RJ, Tousignant CP, Miller DR, Hull KA. Alfentanil controls the haemodynamic response during rapidsequence induction of anaesthesia. Can J Anaesth. 1990 Oct;37(7):755–61.

10. Bruder N, Ortega D, Granthil C. Consequences and PREvention methods of hemodynamic changes during laryngoscopy and INTratrachealintubation. Ann FrAnesthReanim. 1992 [cited 2019 Oct 29];11:57–71.
11. Isaac L. Clonidine in the central nervous system: site and mechanism of hypotensive action. J CardiovascPharmacol. 1980;2Suppl
14. Kothari D, Sharma CK. Effect of nalbuphine and pentazocine on attenuation of hemodynamic changes during laryngoscopy and endotracheal intubation: A clinical study. Anaes Essays Res 2013;7:326-30
15. Tariq AM, Iqbal Z, Qadirullah. Efficacy of nalbuphine in preventing haemodynamic response to laryngoscopy and intubation. J Postgrad Med Inst2014;28:211-6.
16. Agarwal S et al. Comparitive efficacy of intravenous premedication of clonidine versus nalbuphine on intraoperative haemodynamic profile of patients during surgery under general anaesthesia.Int J Res Med Sci.2019 May;7(5):1733-1739
17. Carabine UA, Wright MC, Howe JP, Moore J. Cardiovascular effects of intravenous clonidine.Anaes. 1991;46:634-7
18. Tripathi DC, Shah KS, Dubey SR, Doshi SM, Raval PV. Hemodynamic stress response during laparoscopic cholecystectomy: effect of two different doses of intravenous clonidine premedication. J AnaesthesiolClinPharmacol. 2011;27:475-80
19. Berg AA, Honjol NM, Ramaprabhu NV. Analgesics and ENT surgery. Brit J ClinPharmacol. 1994;38:533-54
20. Kothari D, Sharma CK. Effect of nalbuphine and pentazocine on attenuation of hemodynamic changes during laryngoscopy and endotracheal intubation: a clinical study. Anaes Essays Res. 2013;7:326-30
21. Chawda PM, Pareek, Mayuresh K, Mehta, Ketan D. Effect ofnalbuphine on haemodynamic response to orotracheal 1:S5-19.
12. Giovannitti JA, Thomas SM, Crawford JJ. Alpha-2 adrenergic receptors agonist: a review of current clinical applications. AnesthProg2015;62:31-8.
13. Haq AU, Kazmi EH, Rao ZA. Nalbuphine prevents haemodynamic response to endotracheal intubation. J Coll Physicians Surg Pak 2005;15:668- 70.
intubation. Journal OfAnaesthesiology Clinical Pharmacology. 2010;26(4):458-460
22. Chaudhari MJ, Bhatia U. Efficacy of nalbuphine in preventing haemodynamic response to laryngoscopy and intubation in comparison to clonidine. NHL J Med Sci. 2015;4(1).
23. Nath R, Dutta S, Khandelwal A. Attenuation of Hemodynamic Response during Laryngoscopy and Intubation with Low Dose Intravenous Nalbuphine. J HematolTransfus 2015;3(5):1036-9
24. Bhalerao PM, Thombre SK, Kapse US, Targe KV. Intravenous clonidine for suppression of haemodynamic response to laparoscopy-a prospective randomized, placebo controlled single center study. Int J Adv Med. 2017;4:788-92.
25. Ray M, Bhattacharjee DP, Hajra B, Pal R. Effect of clonidine and magnesium sulphate on anaesthetic consumption, haemodynamicsand postoperative recovery: A comparative study.Ind J Anaesth 2010; 54:137-41.
26. Altan A, Turgut N, Yildiz F, Turkmen A, Ustiin H. Effects of magnesium sulphate and clonidine on propofol consumption, haemodynamics and post- operative recovery. British Journal of Anaesthesia2005;93:438- 41.
27. Zalunardo MP, Zollinger A, Spahn DR, Seifert B, Radjaipour M, Gautschi K, et al. Effect of intravenous and oral clonidine on hemodynamic and plasma catecholamine response due to endotracheal intubation. J ClinAnesth. 1997;9:143-7