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Original Research Article

Comparative efficacy of intravenous premedication of clonidine versus nalbuphine on intraoperative hemodynamic profile of patients during surgery under general anesthesia: a randomized study

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ABSTRACT

Background: Airway manipulation and surgical stimulation lead to variable changes in hemodynamic profile due to increase in plasma catecholamine levels, but these changes can be attenuated by appropriate premedication. The present study was designed to compare the clinical efficacy of intravenous premedication of clonidine with nalbuphine on intraoperative hemodynamic profile of patients during surgery under general anaesthesia.
Methods: Sixty adult consenting patients of ASA physical status I and II of either gender were randomized into two groups of 30 patients each, to receive either intravenous clonidine (2 µg/kg) or nalbuphine (0.2 mg/kg), 10 min before induction with propofol. Direct laryngoscopy and intubation were facilitated with vecuronium bromide. Changes in heart rate, blood pressure and electrocardiogram were recorded at specific time intervals and were noted as primary variable. Any adverse effects and complications were recorded as secondary outcomes.
Results: After laryngoscopy and intubation, the increase in mean heart rate and mean blood pressure occurred immediately in patients of both groups, but persisted up to 6 to 10 min in patients of clonidine group, thereafter the changes returned back to baseline values, while in patients of nalbuphine group, this increase persisted up to 8 to 10 min. The differences in hemodynamic changes between the groups were statistically significant throughout the surgery and post extubation.
Conclusions: Intravenous clonidine was more effective than nalbuphine to attenuate the hemodynamics changes during stressful period of laryngoscopy, intubation and surgery.

Keywords: Airway stimulation, Clonidine, Hemodynamic profile, Nalbuphine

INTRODUCTION

Laryngoscopy and intubation predictably lead to transient and variable tachyarrhythmia and hypertension, while surgical stimulus also leads to an increase in plasma nor-epinephrine and epinephrine levels along with increased plasma renin activity, leading to an increase in cardiac workload. These hemodynamic changes predispose the myocardium to ischemia that may be life threatening in vulnerable patients.[1] The magnitude of hemodynamic changes can be attenuated by narcotic analgesics, α-2 adrenoreceptors agonists, intravenous lidocaine, beta-

blockers, vasodilators and calcium channel blockers but with their inherent side effects of respiratory depression, histamine release and gastrointestinal effects.[2]

Clonidine is a centrally acting partial α-2 adrenergic agonist and decreases the sympathetic outflow from central nervous system to peripheral tissues while peripheral nerve endings inhibit release of nor-epinephrine. It has sedative, analgesic and antihypertensive action along with reduction of the anaesthetic drugs requirement, hence now it becomes trendy to obtund the hemodynamic responses of laryngoscopy and intubation by clonidine premedication. It also minimizes post-operative pain, nausea and vomiting when used as in premedication.[3,4]

Nalbuphine is agonist at κ receptor and acts as antagonist at μ receptor. It exerts its action by inhibiting the release of neurotransmitter to effectively suppress the hemodynamic profile during airway stimulation. Its cardiovascular stability, long duration of analgesia, decreased incidences of respiratory depression and vomiting, makes it an ideal analgesic during anaesthesia.[5,6]

This prospective double-blind randomized study was designed to comparatively evaluate the clinical efficacy of intravenous clonidine versus nalbuphine on intraoperative hemodynamic profile of patients during surgery under general anaesthesia.

METHODS

After approval from Institutional Ethical Committee and written informed consent, 60 patients of American Society of Anaesthesiologists (ASA) physical status I and II of either sex, aged between 18 to 58 years, scheduled for elective surgery under general anesthesia between November 2017 to October 2018, were enrolled for the present double blind randomized study.

The patients suffering from cardio-pulmonary diseases, hepatic disease or renal disease, uncontrolled hypertension, any neurological disorder or endocrinal disease, obesity and patients with anticipated difficult airway or who required more than one attempt for intubation, were excluded from the studies. Patients with known hypersensitivity or drug allergies, taking antihypertensive or antidepressant drugs, were also excluded from the study.

Patients were divided into two equal groups of 30 patients each, according to computer generated random number table. Patients of group I received intravenous clonidine in dose of 2 μg/kg and patients of group II received intravenous nalbuphine in dose of 0.2 mg/kg.

Both study drugs were diluted in 10 ml normal saline and administered intravenously, 10 minutes before induction. Study drug preparation was done by a resident who was blinded to study protocol and was not involved for any data collection.

On arrival to operation theatre, baseline vital parameters of heart rate, non- invasive systemic blood pressure, peripheral oxygen saturation (SpO2) and electrocardiogram (ECG), were commenced. An intravenous line was secured with 18 Gauze intravenous cannula and lactate Ringer solution was started at the rate of 4-6 ml/kg/hr. All patients were premedicated with midazolam 0.02 mg/kg, glycopyrrolate 0.2 mg, followed by study drug-clonidine, 2 μg/kg or nalbuphine, 0.2 mg/kg intravenously, 10 min before induction of anaesthesia in double blind manner.

After pre-oxygenation, anaesthesia was induced with propofol 2 mg/kg, followed by vecuronium bromide 0.1 mg/kg to facilitate the direct laryngoscopy and intubation. Intubation was accomplished by Macintosh curve blade laryngoscope with proper sized cuffed endotracheal tube. Anaesthesia was maintained with isoflurane, nitrous oxide 60% in oxygen. Patients were mechanically ventilated to keep normocapnia (EtCO2 between 35-40 mmHg).

The hemodynamic parameters of heart rate, systemic blood pressure (systolic, diastolic and mean arterial pressure), peripheral oxygen saturation and any changes in cardiac rhythm were recorded at baseline, after giving study drug, after induction with propofol, immediately after laryngoscopy and tracheal intubation and then at 1st, 2nd, 3rd, 5th min, 10th and 15th min after tracheal intubation. Thereafter these changes were recorded at 5 mins interval till the end of surgery and post extubation.

The hemodynamic changes observed as abnormal findings during the study were defined as hypotension when systolic blood pressure was less than 20% of baseline or <90 mmHg. Hypertension was defined when systolic blood pressure was more than 20% of baseline or >140 mmHg. Tachycardia was defined as heart rate >100 beats/min and bradycardia were defined as heart rate <60 beats min.

If intraoperative hypertension and tachycardia occurred, it was managed by increasing the dial concentration of isoflurane. Hypotension was primarily treated by increasing the intravenous infusion rate of lactate ringer solution, and additionally with vasoactive drugs. Bradycardia was treated with bolus of intravenous atropine. Hemodynamic changes occurring during study period were not treated unless these changes were sustained over a period of time and were compromising safety of patients and records of each such patient was kept.

At the end of surgery, isoflurane was discontinued, and residual neuromuscular blockade was antagonized with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). Extubation was performed when respiration

became adequate in tidal volume and patient was able to obey simple commands. Patients were transferred to post anaesthesia care unit and monitored until there were no signs of any drug-induced effects. Any hemodynamic changes, respiratory depression, postoperative shivering, nausea and vomiting was noted and treated accordingly.

Sample size

Preliminary sample size was decided in consultation with statisticians and was based on previous studies, which indicated that approximately 27 patients should be included in each group in order to ensure power of 80% and alpha error of 0.05 with confidence limit of 95% for detecting clinically meaningful reduction by 20 % in hemodynamic parameters during laryngoscopy, endotracheal intubation and during intraoperative period.

Assuming a 5% drop out rate and for equal distribution of patient in both the groups, a total of 60 patient were incorporated in the study for better validation of results. The data obtained in the study was presented in a tabulated manner and variables were expressed as mean±standard deviation (SD), considering the later as the best predictor for statistical analysis.

The results were analyzed using Stat graphic centurion, version 16 (Stat point technologies INC, Warrenton, Virginia). The parameters of both groups were compared using one-way analysis of variance (ANOVA), Chi square test and paired 'T' test. A p value of less than 0.05 was considered to indicate statistical significance.

RESULTS

The present study compared the clinical efficacy of clonidine with nalbuphine for intraoperative hemodynamic profile of patients undergoing surgery under general anaesthesia on 60 adult patients of both genders. There was no protocol deviation and study were successfully completed. Data of all patients were included for statistical analysis. The demographic data for age, weight, genders and American Society of Anaesthesiologist (ASA) physical status were comparable between both the groups (Table 1).

Table 1: Demographic data of the patients.

Demographic parameters	Group I	Group II	P value
Age (years)	47.62±10.4	48.54±9.4	0.07
Weight (kg)	59.17± 7.5	60.83±9.3	0.565
Gender (M/F)	18/11	19/11	0.87
ASA (I/II)	22/8	21/9	0.73

Data are presented in Mean±SD or absolute numbers. P value >0.05 is statistically insignificant.

Hemodynamic changes

At baseline, the mean systolic blood pressure, diastolic blood pressure and heart rate in patients of group I was 128.87±4.36 mmHg, 84.6±7.05 mmHg and 85.6±6.08 beats/min respectively, while in patients of group II, it was127.7±3.15 mmHg, 82.5±6.0 mmHg and 88.57±7.2 beats/min respectively.

Table 2: Comparison of mean heart rate.

Heart Rate (beats/min)	Group I		Group II		P value
	Mean	SD	Mean	SD	
Baseline	85.6	6.08	88.57	7.2	0.090
After study drug	80.63	5.67	89.5	6.32	**<0.001
After Induction	74.97	7.8	83.4	8.54	**<0.001
Immediate post Laryngoscopy & Intubation	96.6	3.2	112.11	5.56	**< 0.001
1 min	92.2	4.6	111.6	5.43	**< 0.001
2 min	90.8	5.9	109.9	5.64	**< 0.001
4 min	90.2	4.6	107.91	5.66	**< 0.001
6 min	88.6	5.2	103.26	5.57	**< 0.001
8 min	85.3	6.4	100.97	6.00	**< 0.001
10 min	84.6	5.6	95.23	5.69	**< 0.001
15 min	84.1	4.8	88.1	6.60	*< 0.05
30 min	81.3	5.0	81.0	6.28	0.757
45 min	80.7	4.82	85.66	6.05	*< 0.05
60 min	80.4	6.36	86.12	5.61	*< 0.05
Post extubation	86.13	6.01	118.34	6.75	*< 0.05

Data are presented in Mean ± SD or absolute numbers;*P value <0.05 is statistically significant; **P value <0.001 is statistically highly significant.

Both groups were comparable and there was no statistically significant difference in the preoperative baseline values. After the administration of clonidine or nalbuphine, the changes in mean heart rate showed highly statistically significant (p <0.001) difference between the groups. There was fall in systolic blood pressure (group I-122.03±8.0 mmHg, group II- 128.67±7.0 mmHg), diastolic blood pressure (group I-80.9±12.49 mmHg, group II-82.7±11.45 mmHg) and mean arterial pressure (group I-94.61±13.11 mmHg, group II-98.0±10.69 mmHg) and the difference was statistically significant (p <0.05) between the groups (Table 2, 3, 4 and 5).

After induction with propofol, there was further decrease in mean heart rate (clonidine group: 74.97±6.99 beats/minute, nalbuphine group- 83.4±8.54 beats/minute) which was statistically highly significant (p=<0.001), systolic blood pressure (clonidine group- 116.2±4.32 mmHg, nalbuphine group- 118.2±4.82 mmHg), diastolic blood pressure (clonidine group: 77.9±13.36 mmHg, nalbuphine group 75.6±10.51 mmHg), and mean arterial pressure (clonidine group: 90.66±14.66 mmHg, nalbuphine group- 89.8±11.92 mmHg), which was comparable between the groups (Table 2, 3, 4 and 5).

Table 3: Comparison of mean systolic blood pressure.

Systolic BP (mm of Hg)	Group I		Group II		P value
	Mean	SD	Mean	SD	
Baseline	127.7	4.36	128.87	3.15	>0.05
After study drug	122.03	8.0	128.67	7.0	*<0.05
After Induction	116.2	4.32	118.2	4.82	0.0764
Immediate post laryngoscopy and intubation	136.8	6.0	137.2	7.68	0.0832
1 min	136.3	5.6	136.4	8.2	0.923
2 min	134.3	4.6	135.2	6.43	0.911
4 min	133.2	4.5	134.9	4.42	0.823
6 min	132.3	4.4	134.7	3.98	0.06
8 min	128.7	5.6	132.3	4.4	*<0.05
10 min	126.3	6.0	130.6	2.75	*<0.05
15 min	118.43	3.6	127.34	3.20	**<0.001
30 min	115.6	4.0	122.7	5.6	**<0.001
45 min	118.2	4.28	123.2	4.6	*<0.05
60 min	121.2	4.0	124.5	3.9	0.076
Post extubation	130.6	3.68	134.3	6.4	0.068

Data are presented in Mean±SD or absolute numbers. *P value <0.05 is statistically significant, **P value <0.001 is statistically highly significant.

Table 4: Comparison of mean diastolic blood pressure.

Diastolic BP (mm of Hg)	Group I		Group II		P value
	Mean	SD	Mean	SD	
Baseline	84.6	7.05	83.5	6.0	0.719
After study drug	80.9	12.49	82.7	11.45	0.069
After Induction	77.9	13.36	75.6	10.51	0.086
Immediate post laryngoscopy and intubation	89.3	8,5	91.4	10.1	*<0.05
1 min	88.07	7.0	90.03	9.92	**<0.001
2 min	86.9	11.3	88.80	10.6	*0.05
4 min	85.7	12.9	87.4	8.32	0.064
6 min	85.3	11.3	87.2	9.5	0.065
8 min	84.6	13.3	85.8	12.025	0.07
10 min	84.2	10.7	85.4	11.497	0.068
15 min	82.3	11.51	84.9	10.93	0.065
30 min	79.8	10.4	84.1	11.19	*0.05
45 min	79.6	12.6	80.46	10.32	*0.05
60 min	82.6	10.85	78.4	10.67	*0.05
Post extubation	84.8	9.76	88.6	5.04	*<0.05

Data are presented in Mean±SD or absolute numbers. *P value <0.05 is statistically significant. **P Value <0.001 is statistically highly significant.

Table 5: Comparison of average mean arterial pressure.

Mean arterial pressure	Group I		Group II		P value
	Mean	Std Dev	Mean	Std Dev	
Baseline	98.96	10.14	98.62	10.74	0.946
After study drug	94.61	13.11	98.0	10.69	*<0.05
After Induction	90.66	14.66	89.8	11.92	0.976
Immediate post laryngoscopy and intubation	102	15.06	106.6	14.32	0.065
1 min	100	16.06	105.4	14.05	*<0.05
2 min	96.7	15.11	104.2	14.26	**<0.001
4 min	92.4	13.41	103.2	12.62	**<0.001
6 min	93	12.53	103.	12.02	**<0.001
8 min	92	15.57	101.3	11.65	**<0.001
10 min	90	15.35	100.4	12.61	**<0.001
15 min	86.34	16.69	99.	12.51	*<0.05
30 min	86.4	14.39	96.9	12.56	*<0.05
45 min	86.4	15.68	94.7	14,54	*<0.05
60 min	88.8	15.45	93.7	12.43	*<0.05
Post extubation	93.4	16.76	103.8	11.95	*<0.05

Data are presented in Mean±SD or absolute numbers. *P value <0.05 is statistically significant. **P Value <0.001 is statistically highly significant.

After laryngoscopy and tracheal intubation, the increase in mean heart rate (96.6±3.2beats/minute), systolic blood pressure (136.8±6 mmHg), diastolic blood pressure (89.3±7.81 mmHg) and mean arterial pressure (106.6±14.32 mmHg), occurred immediately after laryngoscopy and intubation in patients of clonidine group and persisted up to 6 to 10 minutes, thereafter the changes returned back to baseline values (Table 2, 3, 4 and 5).

After laryngoscopy and tracheal intubation, the increase in mean heart rate (112.11±5.56 beats/minute), systolic blood pressure (137.7±7.68 mmHg), diastolic blood pressure (91.4±5.87 mmHg) and mean arterial pressure (106.6±14.32 mmHg) occurred immediately after laryngoscopy and intubation in patients of nalbuphine group and persisted up to 8 to10 minutes, thereafter the changes returned back to baseline values (Table 2, 3, 4 and 5).

Post extubation, there was increase in mean heart rate (clonidine group- 86.13±6.01 beats/minute, nalbuphine group: 118.34±6.75 beats/minute) which was statistically highly significant (p=<0.001), systolic blood pressure (clonidine group: 130.6±3.68 mmHg, nalbuphine group-134.3±6.4 mmHg), diastolic blood pressure (clonidine group: 84.8±9.76 mmHg, nalbuphine group 88.6±5.04 mmHg) and mean arterial pressure (clonidine group-93.4±16.76 mmHg, nalbuphine group: 103.8±11.95 mmHg), with statistically significant difference between both the group (Table 2, 3, 4 and 5).

DISCUSSION

Endotracheal intubation and intraoperative surgical stress initiates sympathetic over activity, leading increased heart rate, blood pressure and occasional dysrhythmias. The therapeutic armamentarium to counteract these cardiovascular responses includes a wide variety of drugs, techniques and route.[7] The significance of the study lies in the fact to select the better drug for premedication which could attenuate the hemodynamic pressor response during laryngoscopy, endotracheal intubation and intraoperative surgical stress.

In the present study, comparative efficacy of intravenous clonidine versus nalbuphine premedication was evaluated for changes in hemodynamic profile during laryngoscopy, intubation, surgical stress and extubation. Both, clonidine and nalbuphine has prevented the marked increase in hemodynamic pressor response to laryngoscopy and intubation.

Clonidine is alpha-2 agonists and showing effects on blood pressure and heart rate, due to its sympatho-inhibitory action. It has analgesic, sedative and anxiolytic profile. Its antinociceptive action exits for both somatic and visceral pain. These properties along with its ability to maintain intra-operative hemodynamic stability make clonidine a useful adjuvant in anaesthesia and intensive care.[8,9]

Nalbuphine, a synthetic and potent agonist/antagonist analgesic with a low abuse potential and causes less respiratory depression by activating the supraspinal and spinal kappa receptor. 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.[10,11]

Carabine UA et al, studied the effect of clonidine on the pressor 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 in patients of both clonidine groups with statistically significant difference among the group, which indicated that the lower dose of clonidine is also appropriate.[12]

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 1 µg/kg, while clonidine in dose of 2 µg/kg, prevented the hemodynamic stress response to pneumoperitoneum along with that of intubation and extubation.[13] So, for the present study, clonidine in dose of 2 µg/kg was selected to attenuate the hemodynamic response.

Nalbuphine has been used in doses of and 0.3 mg/kg by Berg AA et al, to prevent the marked rise in heart rate and blood pressure during laryngoscopy and intubation.[14] Kothari D et al, have administered 0.2 mg/kg nalbuphine to attenuate the hemodynamic responses.[15] So in this study, nalbuphine was used in dose of 0.2 mg/kg which possess less side effects like nausea, vomiting and postoperative respiratory depression.

In the present study, clonidine and nalbuphine were given 10 minutes before induction which is an optimum time to administer these drugs to protect against circulatory response to laryngoscopy and tracheal intubation and for intraoperative surgical stress.

Chawda PM et al, studied the efficacy of nalbuphine in preventing the increase in heart rate and mean arterial pressure in response to laryngoscopy and intubation and 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 to 8 min but always remained higher than patient of nalbuphine group. Therefore, they concluded that nalbuphine attenuated haemodynamic response to laryngoscopy and intubation.[16]

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.[17]

Zalunardo MP et al, compared the oral clonidine with intravenous clonidine 3 µg /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 oral clonidine group.[18]

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.[19] 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. Based on the results of the present study and the above discussion, 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.

CONCLUSION

The therapeutic armamentarium to counteract the cardiovascular responses to laryngoscopy and intubation includes a wide variety of drugs, technique and route of administration. Intravenous premedication with clonidine was more effective than nalbuphine at 0.2 mg/kg for attenuation of hemodynamic stress response during laryngoscopy, intubation and surgical stimulation in intraoperative period.

The dose of propofol required for induction of anesthesia and intraoperative isoflurane concentration for each patient could have been assessed as clonidine and nalbuphine, both causes sedation.

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