COMPARATIVE EVALUATION OF THE EFFICACY OF NALBUPHINE PREMEDICATION TO INTRAVENOUS CLONIDINE ON HEMODYNAMIC ALTERATIONS DURING DIRECT LARYNGOSCOPY AND INTUBATION

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Background: The use of accurate medicine can help in the modification of the accentuated hemodynamic changes reported during direct laryngoscopy. These hemodynamic changes can lead to ischemia in the myocardium which can threaten life in subjects with compromised cardiac status. Administration of adequate premedication, rapid intubation, and smooth induction can reduce such risk.

Aim: The study aimed to comparatively evaluate the efficacy of nalbuphine premedication to intravenous clonidine on hemodynamic alterations during direct laryngoscopy and intubation.

Methods: The study assessed 120 subjects divided randomly into two groups of 60 subjects each where Group I was given 2 μg/kg Clonidine and Group II subjects were given 0.2 mg/kg nalbuphine 10 minutes before anesthesia induction intravenously. Vecuronium bromide helped in intubation using direct laryngoscopy and standardized anesthetic technique. Alterations in ECG, blood pressure, and heart rate was assessed at baseline, after drug, laryngoscopy, and

intubation, after 1, 2, 3, 5, 10, and 15 minutes after intubation. Complications and side effects were also assessed.

Results: Following premedication, a significant difference was seen in the fall of blood pressure and heart rate in the two groups. Following intubation and laryngoscopy, an immediate increase was seen in mean blood pressure and heart rate for both groups which remained for 5-7 minutes in the Clonidine group and 10 minutes in the nalbuphine group with an intergroup significant difference.

Conclusion: Premedication with 2 μg/kg intravenous clonidine helps in effectively reducing the hemodynamic alterations during intubation and direct laryngoscopy in comparison to 0.2 mg/kg intravenous nalbuphine given 10 minutes before the induction.

Keywords: Clonidine, Direct Laryngoscopy, Hemodynamic changes, Intubation, Nalbuphine

Introduction

Airway manipulation methods including endotracheal intubation, laryngoscopy, and other techniques act as noxious stimuli that can lead to considerable changes in the physiology of the cardiac system through the response of the reflexes. The resultant increase in the blood pressure and pulse rate is generally unpredictable, variable, and transitory and has detrimental outcomes including cerebral hemorrhage and myocardial ischemia.[1]

Presently, surgeries have become common and play a vital role in higher life expectancy. However, the surgical procedures had been associated with significant changes in the hemodynamic parameters resulting in reduced cardiac output secondary to increased pulmonary and systemic vascular resistance, increased mean arterial pressure, and an increase in the heart rate. In susceptible subjects, these alterations in the hemodynamic parameters result in ischemic changes. Various drugs and techniques as anesthesia of higher depths have been assessed to reduce the adverse impact of hemodynamic parameters.[2]

The process of intubation and direct laryngoscopy is usually conducted to preserve the airway from aspiration and allow ventilation without interruption during the state of general anesthesia. However, despite of significant clinical advantages of these procedures, they are associated with various side effects owing to a raise in catecholamine concentration in the plasma which can further cause hypertension and tachyarrhythmia in the subjects.[3] The changes in the hemodynamic parameters expose the myocardium to the ischemic changes that can threaten life

in subjects having compromised cardiac state. Administration of adequate premedication, rapid intubation, and smooth induction can help in reducing the risks associated with the alterations in the hemodynamic parameters. An anesthetic technique or drug is considered ideal when it has minimal alterations in the hemodynamic parameters, is convenient and safe to administer and prepare, and has rapid action of onset.[4] These ideal properties of anesthetic drugs should be the same for the subjects of all age groups, avoid awareness during anesthesia conditions, and should not impair cerebral blood flow. Also, it should not affect recovery parameters and anesthesia duration.[5]

Nalbuphine is an anesthetic agent which is a semi-synthetic opioid analgesic from the agonist-antagonist class. Nalbuphine is an antagonist at mu (μ) receptors and is an agonist for (κ) receptors. Nalbuphine helps in providing hemodynamic stability during the intraoperative period along with the suppression of the hemodynamic response. Nalbuphine has a ceiling effect in respiratory depression imposing its potential safety during the conditions of overdose which makes nalbuphine an ideal anesthetic agent.[6]

Another anesthetic agent, Clonidine is a partial α2 adrenergic agonist that leads to a decrease in the outflow of the sympathetic nervous system from the central nervous system to the peripheral tissues that further stops the norepinephrine release. Clonidine has antihypertensive, analgesic, and sedative effects along with reducing the need for anesthetic drug use.[7]

The present prospective clinical study was done to comparatively evaluate the efficacy of nalbuphine premedication to intravenous clonidine on hemodynamic alterations during direct laryngoscopy and intubation.

Materials and Methods

The present prospective randomized clinical study was done to comparatively evaluate the efficacy of nalbuphine premedication to intravenous clonidine on hemodynamic alterations during direct laryngoscopy and intubation. The study was done at Department of Anaesthesiology, Shri Shankaracharya Institute of Medical Sciences, Bhilai, Durg, Chhattisgarh. The study population was selected from the subjects undergoing direct laryngoscopy and intubation in the institute. After explaining the detailed study design, informed consent in both verbal and written format was taken from all the subjects.

The inclusion criteria for the study were subjects undergoing elective surgery under general anesthesia in the institute, subjects of ASA physical status I and II, weighing 50 kgs ad 72 kgs, and subjects aged 18 years to 60 years. The exclusion criteria were subjects that were not willing to study participate, subjects for whom more than one attempt was made for intubation, subjects with a difficult airway, subjects on medication, drug allergy, drug allergy, obesity causing morbidity, endocrine disease, neurologic disease, renal disease, hepatic disease, untreated or uncontrolled diabetes mellitus, and/or cardiopulmonary diseases.

The study included 120 adult subjects that were randomly divided into two groups of 60 subjects each based on the flip-of-the-coin method. Group, I subjects were administered 2 μg/kg Clonidine and Group II subjects were given 0.2 mg/kg Nalbuphine via intravenous route as premedication. Both Clonidine and Nalbuphine were given in 10ml normal saline as diluted drugs 10 minutes before induction of anesthesia. The subjects were divided and the drugs were prepared by an expert person unaware of the study procedure.

Technique of Anesthesia

Following inclusion, all the subjects were administered 0.25 mg of Alprazolam. One night before surgery, Ranitidine in 150 grams oral dose was given one night before the surgery and was kept NPO 6 hours before the surgery. After the subject was brought to the operation room, all subjects were monitored for routine examination and vital parameters in the supine position including ECG (electrocardiogram), SpO2 (peripheral oxygen saturation), blood pressure, and heart rate of the participants. This was followed by securing the IV (intravenous) line and infusion of Ringer lactate solution at 4-6ml/kg/h.

The subjects were injected with 4mg ondansetron, 100 μg Fentanyl, 0.2mg glycopyrrolate, and 0.02mg/kg midazolam. This was followed by the administration of intravenous 2 μg/kg of Clonidine or 0.2mg/kg nalbuphine solution depending on the group being treated 10 minutes before anesthesia induction based on the schedule of randomization. Pre-oxygenation was done with 100% oxygen using a face mask for 3 minutes followed by anesthesia induction using 2mg/kg propofol and 0.1mg/kg vecuronium to allow intubation and direct laryngoscopy. Within 15 seconds of zero TOF (train of four), laryngoscopy was done utilizing cuffed endotracheal tube. Maintenance of anesthesia was done with 60% nitrous oxide in oxygen and isoflurane. Normocapnia was maintained by mechanical ventilation.

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The hemodynamic parameters including the ECG (electrocardiogram), peripheral oxygen saturation, systemic blood pressure, and heart rates were assessed at baseline, following administration of study drugs, following laryngoscopy, immediately following intubation, at 1, 3, 5, 7, 10, and 15 minutes following intubation. These were then monitored every 5 minutes during the operative time till the completion of surgery and extubation.

Hemodynamic alterations were assessed as abnormal when subjects had a change in blood pressure where hypertension was considered when systolic blood pressure was 140mmHg or more or was 20% higher than baseline values and hypotension was considered when systolic blood pressure was 90mmHg or lower or systolic blood pressure was less than 20% of baseline values. Tachycardia and bradycardia were evaluated as heart rates of 100 beats/minute or 60 beats/minute. Hemodynamic alterations during the study were not managed unless they persisted for a long time and were threatening to the subjects. Appropriate measures were taken to manage hemodynamic parameters wherever needed.

After completion of the surgery, isoflurane was stopped followed by the administration of 0.01mg/kg glycopyrrolate and 0.05mg/kg neostigmine as an antagonist to neuromuscular blockade. To assess the adequacy of the reflexes, neuromuscular transmission and consciousness levels were assessed. After ensuring adequate anesthesia reversal, the subjects were extubated and were following the instructions. The hemodynamic parameters, postoperatively assessed were vomiting, nausea, respiratory depression, sedation, shivering, and hemodynamic events and were managed as needed.

The data gathered were assessed statistically and the results were expressed as mean and standard deviations. For data assessment, SPSS software version 25.0 (IBM Corp., Armonk, NY) for the two study groups. The data for the two groups were compared using ANOVA (analysis of variance), t-test (paired and unpaired), and the chi-square test. The significance threshold was kept at a p-value of less than 0.05 and a p-value of <0.001 was taken as a highly significant result.

Results

The present prospective randomized clinical study was done to comparatively evaluate the efficacy of nalbuphine premedication to intravenous clonidine on hemodynamic alterations

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during direct laryngoscopy and intubation. The study included 120 adult subjects that were randomly divided into two groups of 60 subjects each based on the flip-of-the-coin method. Group, I subjects were administered 2 μg/kg Clonidine and Group II subjects were given 0.2 mg/kg Nalbuphine via intravenous route as premedication. The demographic and study data at baseline for two groups of study subjects are summarized in Table 1. At baseline, the mean age, ASA status, gender, mean weight, mean height, mean arterial pressure diastolic blood pressure, systolic blood pressure, and heart rate had non-significant differences between the two groups with respective p-values of 0.08, 0.78, 0.85, 0.54. 0.46, 0.92, 0.23, 0.21, and 0.08 (Table 1).

For the changes in the hemodynamic parameters, and for systolic blood pressure, the results are depicted in Table 2. At baseline, systolic blood pressure was 128.85±4.34 mmHg and 127.5±3.13mmHg respectively for groups I and II which was statistically comparable with $p>0.05$. After administering the study drug, a significant increase was seen for Group I to 122.01±8.2mmHg and Group II to 128.65±7.2 which was signed between the two groups with $p<0.05$. After induction, a significant decrease was seen in two groups where the intergroup difference was statistically significant with $p=0.03$. However, immediately following intubation, a significant increase was seen to 136.6±5.8 and 137.4±7.66 mmHg in Group I and II respectively. This difference was statistically significant with $p=0.02$. The difference in systolic blood pressure was statistically significant at 2, 3, and 5 minutes with respective p-values of 0.01, 0.02, and 0.05. The systolic blood pressure then decreased for both the groups at 7, 10, and 15 minutes with a p-value of <0.05 for all.

Concerning the diastolic blood pressure in the two groups of study subjects, it was comparable in the two groups at baseline with 84.4±7.03 and 85.1±6.2 respectively and $p>0.05$. After drug administration, in both groups, diastolic pressure decreased significantly with $p<0.05$. Similarly, a decrease was noted after induction ($p<0.05$). However, immediately following intubation, an increase was seen in both groups with $p<0.05$. After 1, 2, 3, 5, 7, and 10 minutes, the difference was significant between the two groups with <0.05. However, for 15 minutes, a decrease was seen in both groups at 15 minutes with $p<0.05$ as shown in Table 3.

On assessing the changes in the heart rate, a comparable value was seen in two groups with 84.4±7.03 and 85.1±6.2 and $p=0.08$. After drug administration, a decrease was seen in both groups to 80.61±5.65 and 86.3±6.34 beats/minute with $p<0.001$. After induction, a decrease in

heart rate was seen for groups with p<0.05. The heart rate in both groups continued to decrease at 1, 2, 3, 5, 7, 10, and 15 minutes after administration of both clonidine and nalbuphine. This showed a statistically significant difference in both the groups at all these time intervals with p-values of <0.05 at all the time intervals as depicted in Table 4.

Concerning the complications seen with the anesthetic drugs in the two groups of study subjects, in Group I where clonidine was given, 10 patients were seen to have hypotension, and in 4 subjects heart rate was reduced to less than 60 beats per minute. These alterations were seen following the premedication. However, an increase was seen in blood pressure and heart rate following intubation and laryngoscopy. No medical care was needed for any subject reported with any complication. No other complication was seen in any subject related to the anesthetic agent given in the present study.

Discussion

The present study assessed 120 adult subjects that were randomly divided into two groups of 60 subjects each based on the flip-of-the-coin method. Group, I subjects were administered 2 μg/kg Clonidine and Group II subjects were given 0.2 mg/kg Nalbuphine via intravenous route as premedication. The demographic and study data at baseline for two groups of study subjects are summarized in Table 1. At baseline, the mean age, ASA status, gender, mean weight, mean height, mean arterial pressure diastolic blood pressure, systolic blood pressure, and heart rate had non-significant differences between the two groups with respective p-values of 0.08, 0.78, 0.85, 0.54. 0.46, 0.92, 0.23, 0.21, and 0.08. These characteristics were comparable to the previous studies of Haq AU et al[8] in 2005 and Dhabi P et al[9] in 2014 where authors assessed subjects with demographics comparable to the present study for hemodynamic changes following the anesthesia administration.

On assessing the changes in the hemodynamic parameters, for systolic blood pressure, the results showed that at baseline, systolic blood pressure was 128.85±4.34 mmHg and 127.5±3.13mmHg respectively for groups I and II which was statistically comparable with p>0.05. After administering the study drug, a significant increase was seen for Group I to 122.01±8.2mmHg and Group II to 128.65±7.2 which was signed between the two groups with p<0.05. After induction, a significant decrease was seen in two groups where the intergroup difference was statistically significant with p=0.03. However, immediately following intubation, a significant

increase was seen to 136.6±5.8 and 137.4±7.66 mmHg in Group I and II respectively. This difference was statistically significant with p=0.02. The difference in systolic blood pressure was statistically significant at 2, 3, and 5 minutes with respective p-values of 0.01, 0.02, and 0.05. The systolic blood pressure then decreased for both the groups at 7, 10, and 15 minutes with a p-value of <0.05 for all. These results were consistent with the findings of Kothari D et al[10] in 2013 and Arora S et al[11] in 2015 where the authors reported similar changes in blood pressure following the administration of clonidine and nalbuphine in their study subjects.

For the diastolic blood pressure in the two groups of study subjects, it was comparable in the two groups at baseline with 84.4±7.03 and 85.1±6.2 respectively and p>0.05. After drug administration, in both groups, diastolic pressure decreased significantly with p<0.05. Similarly, a decrease was noted after induction (p<0.05). However, immediately following intubation, an increase was seen in both groups with p<0.05. After 1, 2, 3, 5, 7, and 10 minutes, the difference was significant between the two groups with <0.05. However, at 15 minutes, a decrease was seen in both groups at 15 minutes with p<0.05. These findings were in agreement with the studies of Tariq AM et al[12] in 2014 and Fating D et al[13] in 2016 where authors suggested similar alterations following nalbuphine in diastolic pressure for the participants of their studies.

Concerning the assessment of the changes in the heart rate, a comparable value was seen in two groups with 84.4±7.03 and 85.1±6.2 and p=0.08. After drug administration, a decrease was seen in both groups to 80.61±5.65 and 86.3±6.34 beats/minute with p<0.001. After induction, a decrease in heart rate was seen for groups with p<0.05. The heart rate in both groups continued to decrease at 1, 2, 3, 5, 7, 10, and 15 minutes after administration of both clonidine and nalbuphine. This showed a statistically significant difference in both the groups at all these time intervals with p-values of <0.05 at all the time intervals. These results were in line with the previous studies of Deepshikha C et al[14] in 2011 and Jiwanmall M et al[15] in 2017 where authors reported the alterations in hemodynamic parameters following the administration of Clonidine and Nalbuphine.

On recording the complications seen with the anesthetic drugs in the two groups of study subjects, in Group I where clonidine was given, 10 patients were seen to have hypotension, and in 4 subjects heart rate was reduced to less than 60 beats per minute. These alterations were seen following the premedication. However, an increase was seen in blood pressure and heart rate

following intubation and laryngoscopy. No medical care was needed for any subject reported with any complication. No other complication was seen in any subject related to the anesthetic agent given in the present study. The assessment of these complications was similar to the studies by Altan A et al[16] in 2005 and Bhalerao PM et al[17] in 2017 where authors suggested hypotension and bradycardia in their study subjects as complications following anesthesia administration.

Conclusion

Considering its limitations, the present study concludes that Premedication with 2 μg/kg intravenous clonidine helps in effectively reducing the hemodynamic alterations during intubation and direct laryngoscopy in comparison to 0.2 mg/kg intravenous nalbuphine given 10 minutes before the induction. However, further studies are needed on multi-institutional setup and a large sample size can help draw a definitive conclusion.

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TABLES

Characteristics	Group I	Group II	p-value
Mean age (years)	46.74±12.5	48.52±10.7	0.08
ASA status			
I	40	42	0.78
II	20	18	
Gender			
Males	36	38	0.85
Females	24	22	
Mean weight (kg)	59.15±7.7	60.21±5.1	0.54
Mean Height (cm)	154.65±4.6	153.81±5.2	0.46
Mean Arterial Pressure (mmHg)	98.94±10.12	98.64±10.72	0.92
Diastolic BP (mmHg)	84.4±7.03	85.1±6.2	0.23
Systolic BP (mmHg)	128.85±4.34	127.5±3.13	0.21
Heart rate (beats/min)	85.4±6.06	89.55±7.4	0.08

Table 1: Baseline characteristics and hemodynamic parameters in study subjects

Systolic blood pressure	Group I	Group II	p-value
Baseline	128.85±4.34	127.5±3.13	>0.05
After drug administration	122.01±8.2	128.65±7.2	<0.05
After induction	116.4±4.34	118.4±4.84	0.03
Immediately after intubation	136.6±5.8	137.4±7.66	0.02
1 min	136.1±5.4	136.2±8.4	0.02
2 min	132.1±4.4	135.4±6.45	0.01
3 min	132.4±4.3	134.5±3.96	0.02
5 min	131.1±4.2	134.5±3.96	0.05
7 min	128.5±5.4	132.1±4.2	<0.05
10 min	126.1±6.2	130.4±2.73	<0.05
15 min	118.41±3.4	127.32±3.22	<0.05

Table 2: Comparison of systolic blood pressure in two study groups

Diastolic blood pressure	Group I	Group II	p-value
Baseline	84.4±7.03	85.1±6.2	>0.05
After drug administration	80.7±12.47	83.5±11.3	<0.05
After induction	76.7±13.34	78.4±10.49	<0.05
Immediately after intubation	89.1±8.3	89.1±8.3	<0.05
1 min	88.05±6.8	91.2±10.3	<0.05
2 min	86.7±11.1	91.4±9.4	<0.05
3 min	85.5±12.7	92.4±7.6	<0.05
5 min	85.1±11.1	90.6±8.4	<0.05
7 min	84.4±13.1	89.6±9.4	<0.05
10 min	84.4±10.5	93.6±7.7	<0.05
15 min	82.1±11.53	94.4±8.2	<0.05

Table 3: Comparison of diastolic blood pressure in two study groups

Heart rate	Group I	Group II	p-value
Baseline	85.4±6.06	89.55±7.4	0.08
After drug administration	80.61±5.65	86.3±6.34	<0.001
After induction	74.95±7.6	83.2±8.52	<0.05
Immediately after intubation	96.4±3.4	112.13±5.54	<0.05
1 min	92.2±4.4	111.4±5.41	<0.05
2 min	90.6±5.7	109.7±5.62	<0.05
3 min	90.4±4.4	107.93±5.64	<0.05
5 min	88.4±5.4	103.24±5.57	<0.05
7 min	85.1±6.2	100.95±6.02	<0.05
10 min	84.4±5.4	95.21±5.67	<0.05
15 min	84.3±4.6	88.3±6.62	<0.05

Table 4: Comparison of mean heart rate in two study groups