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Original Research Article

Comparative study of two different doses of nalbuphine attenuating hemodynamic response to laryngoscopy and intubation in patients undergoing general anesthesia

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ABSTRACT

Background: Various anaesthetic agents have been tried to attenuate pressor response to laryngoscopy and intubation. Among the recommended groups intravenous nalbuphine satisfies without much undesired effects. The objective was to study efficacy of two different doses of nalbuphine to attenuate pressor response to laryngoscopy and intubation.
Methods: This was hospital based comparative study was carried out at Karnataka institute of Medical Sciences Hospital, Hubli, India. Patients were divided into two groups of 50 each randomly. First group was named as N1 and the second group was named as N2. Patients in N1 were given 0.1mg/kg Nalbuphine in 10ml of normal saline and patients in N2 were given 0.2-0.1mg/kg Nalbuphine in 10ml of normal saline. Appropriated statistical tests were applied like t test, ANOVA. P value if found less than 0.05 was recorded as statistically significant.
Results: There was marked increase in HR, SBP, DBP and MAP immediately following laryngoscopy and intubation in the both the groups. Intravenous Nalbuphine given 5 minutes before intubation in the dose of 0.2mgkg^{-1} body weight effectively attenuated the hemodynamic response after laryngoscopy and intubation. However, there was a rise in HR, SBP, DBP and MAP immediately following intubation in group N2 which was clinically not significant though statistically significant. Side effects like nausea, vomiting, respiratory depression and sedation was not observed in both study groups.
Conclusions: Authors concluded that 0.2mg/kg body weight dose of Nalbuphine was found to be more effective than 0.1mg/kg body weight dose of nalbuphine in maintaining the haemodynamics of the patients.

Keywords: Efficacy, Haemodynamics, Intubation, Laryngoscopy, Nalbuphine

INTRODUCTION

Laryngoscopy and intubation are often associated with significant increase in blood pressure and heart rate which can be detrimental to patients with cardiovascular comorbid diseases such as hypertension, ischemic heart disease and also in patients with central nervous system pathology. Whenever a patient undergoes surgery and whenever that surgery has to be performed under general anesthesia, then as a rule, there is need to perform intubation and laryngoscopy. These things can lead to changes in hemodynamics of the patient as a result that the catecholamines are released into the systemic circulation.[1,2] Various factors influence the pressor

response to laryngoscopy and intubation such as presence of hypertension, IHD, inadequate depth of anesthesia etc. It also depends upon the type of agent used for anesthesia. Time taken for laryngoscopy and intubation also influences this phenomenon. Fortunately, these hemodynamic changes are transient, however, it is difficult to predict as to which patient will have significant hemodynamic response. In majority of ASA grade 1 and 2 patients it is not associated with adverse effects and does not lead to a bad outcome. However, as mentioned earlier these hemodynamic changes can adverse effects on patients with comorbid conditions such as hypertension, ischemic heart disease etc.[3,4]

In such patients with preexisting diseases and undergoing surgery under general anesthesia, there is chance that they may develop myocardial ischemia, stroke or pulmonary edema.[5,6]

Various agents such as beta blockers, NTG, various opioids, lignocaine etc., have been tried to attenuate hemodynamic response to laryngoscopy and intubation during general anesthesia. Among the recommended groups, intravenous nalbuphine satisfies without much undesired effects. Nalbuphine is a potent agonist-antagonist opioid which can be used for this purpose.[7]

Nalbuphine is a synthetic opioid agonist-antagonist analgesic related chemically to the opioid oxymorphone and to opioid antagonist naloxone. It is primarily a kappa receptor agonist and mu receptor antagonist analgesic. Nalbuphine has an analgesic (agonist action) potency equivalent to that of morphine on milligram basis and its antagonist activity (reversal of major effects of opioid drugs) is about one-fourth of that of Nalorphine and ten times that of Pentazocine. Nalbuphine is highly lipid soluble and metabolized in liver, its onset of action is 3-5 minutes after intravenous administration, and plasma half- life is 3-6 hours. It has only minor and common side effects like vomiting or nausea. Sedation is the most common side effect which is seen in one-third of the patients. Injection Nalbuphine is available in India as NACPHIN 20mg/ml (NEON) and can be used through intravenous route for attenuation of sympathetic response to laryngoscopy and intubation. Not many studies have been done in India using nalbuphine in the parenteral form for attenuation of intubation response.[8]

Present study was an attempt to study efficacy of nalbuphine on hemodynamics during laryngoscopy and intubation in two different doses.

METHODS

This was hospital based comparative study carried out at Karnataka institute of medical sciences hospital, Hubli, India from January 2016 to December 2016. Ethical committee clearance was taken before the study began. Patients were well informed about the nature of the present study and their informed consent was taken. About 100 patients fitting into the inclusion and exclusion criteria designed for the present study.

Patients of age 18-60 years, with ASA grade I and II, elective surgeries only, use of general anesthesia during the surgery were included.

Whenever author suspected that airway of the patient may be difficult, known cases of hypersensitivity to the study drug, those patients were excluded.

Patients were divided into two groups of 50 each randomly. Randomization was done using computer generated randomization table. First group was named as N1 and the second group was named as N2. Patients in N1 were given 0.1mg/kg Nalbuphine in 10ml of normal saline and patients in N2 were given 0.2-0.1mg/kg Nalbuphine in 10ml of normal saline.

Procedure

All patients underwent pre-anesthetic evaluation one day prior to surgery. They received 10mg diazepam and 150mg ranitidine per orally at night time before surgery. Intraoperative monitoring included electrocardiogram, pulse oximetry, noninvasive blood pressure and EtCO2.

The baseline hemodynamic parameters such as heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure were recorded. Five minutes before induction the study drug i.e. either 0.1mg/kg or 0.2mg/kg depending on the group they belonged to was administered intravenously. All the patients were pre-medicated with injection glycopyrrolate 0.2mg, injection midazolam 0.05mg/kg^{-1} before pre-oxygenation. Then patients were pre-oxygenated for 3 minutes via a face mask with Bains circuit.

Anesthesia was induced with protocol as a 1% solution at 2mg/kg^{-1} dose. Endotracheal intubation was facilitated with 2mg/kg^{-1} I.V. succinylcholine one minute prior to laryngoscopy and intubation. 5 minutes after giving study drug, laryngoscopy and intubation was performed by a senior anesthetist using Macintosh no. 3 or 4 blades.

Anesthesia was maintained using 66% nitrous oxide and 33% of oxygen with propofol infusion at 100mcg/kg^{-1}. After the patients recovered from succinylcholine further neuromuscular blockade was maintained with vecuronium 0.1mg/kg^{-1}. No surgical or any other stimulus was applied during 10 minutes of study period and vecuronium was the only additional drug given during 15 minutes period. At the end of the procedure patients were reversed with neostigmine 0.05mg/kg^{-1} I.V. and glycopyrolate 0.0 mg/kg^{-1} I.V.

The following parameters were monitored during the study period i.e. heart rate, systolic blood pressure, diastolic blood pressure mean blood pressure. The above parameters were recorded at baseline (T0), three minutes

after giving the study drug (T1), immediately after induction and intubation (T2), one minute after intubation (T3), two minute after laryngoscopy and intubation (T4), three minutes after laryngoscopy and intubation (T5), four minutes after laryngoscopy and intubation (T6), five minutes after laryngoscopy and intubation (T7), ten minutes after laryngoscopy and intubation (T8). Appropriated statistical tests were applied like t-test, ANOVA. P value if found less than 0.05 was recorded as statistically significant.

RESULTS

Table 1 shows distribution of parameters among the two groups. The mean age in group N1 and group N2 were 36.1±10.8 and 34.4±11.5 respectively. The mean body weight in Group N1 was 59.3±7.3 and in Group N2 it was 57.7±6.4. The age and weight of patients in two groups were comparable (p>0.05). It has been observed that there was no statistical significance difference in age and ASA distribution within the interventional groups.

Table 1: Distribution of parameters among the two groups.

Parameters		Group N1	Group N2	T value or $\chi 2$ value	P value
Age (years)		36.1±10.8	34.4±11.5	0.7620	0.4479
Weight (kg)		59.3±7.3	57.7±6.4	1.1654	0.2467
Sex	Male	25 (50%)	25 (50%)	0.00	0.99
	Female	25 (50%)	25 (50%)		
ASA grade	I	46 (92%)	44 (88%)	0.44	0.51
	II	4 (8%)	6 (12%)		

Table 2: Heart rate variation (in beats per minute).

Drug/Time	0.1mg Nalbuphine				0.2mg Nalbuphine			
	No.	Mean	SD	Mean difference[a]	No.	Mean	SD	Mean difference[a]
T0	50	94.16	16.37	-	50	92.28	17.10	-
T1	50	92.00	16.94	2.16	50	93.84	18.21	-1.56
T2	50	107.64	12.29	-13.48	50	110.16	15.84	-17.88
T3	50	103.84	11.87	-9.68	50	101.96	16.04	-9.68
T4	50	101.16	11.43	-7.00	50	101.68	13.34	-9.40
T5	50	99.94	10.26	-5.78	50	100.70	12.46	-8.42
76	50	97.36	11.34	-3.20	50	114.78	112.24	-22.50
T7	50	96.68	11.08	-2.52	50	97.08	12.66	-4.80
T8	50	95.40	10.31	-1.24	50	96.58	12.03	-4.30

'a' denotes mean difference calculated with basal levels measured at T0, repeated measures ANOVA and factorial ANOVA used, effect of time (F value=3.5, p<0.01), Drugs (F value=1.3, p=0.24) and drug*time interaction (F value=0.97, p =0.45) Values in bold indicates statistically significant difference, p-value <0.05 was significant.

Table 2 shows intra group variability of mean heart rate. In group N1, base line HR was 94.16±16.37, after premedication with study drug at 3 minutes was 92.00±16.94 and immediately after induction and intubation was 107.64±12.29. The mean HR rise was 13.48 which were statistically significant. And there after HR at every minute for next 3 minutes gradually reduced with mean rise of 9.68 (T3), 7.00 (T4) and 5.78 (T5). This was statistically significant. In group N2, base line HR was 92.28±17.10, after premedication with study drug at 3 minutes was 93.84±18.21 and immediately after induction and intubation was 110.16±15.84. The mean HR rise was 17.88 which were statistically significant and there after HR at every minute for next 3 minutes gradually reduced with mean reduction of 9.68 (T3), 9.40 (T4) and 8.40 (T5). Which was statistically non-significant. At T6 the rise of mean HR was 22.50 which were statically significant. At the end of the study, after ten minutes of intubation, the mean HR rise was not statically significant. The mean HR rise in both the groups during the study was not clinically significant.

Table 3 shows intra group variability of mean systolic blood pressure (SBP). In group N1, baseline BP was 125.74±12.76, after premedication with study drug at 3 minutes was 119.82±13.17 and immediately after induction and intubation was 134.30±18.01. The mean SBP rise was 8.56 which were statistically significant. And there after mean SBP at every minute for next 5 minutes gradually reduced with mean SBP reduction of 5.78 (T3), 9.64 (T4), 11.58 (T5), 13.74 (T6), 14.08 (T7) and after 10 minutes after intubation was 14.38 (T8),

which was statistically significant. In group N2, base line SBP was124.22±14.62, after premedication with study drug at 3 minutes was 116.24±13.15 and immediately after induction and intubation was 133.76±21.02. The mean SBP rise was 9.54 which were statistically significant and there after mean SBP at every minute for next 5 minutes gradually reduced with mean reduction of 5.12 (T3), 11.62 (T4), 12.06 (T5), 14.66 (T6), 14.56 (T7) and after 10 minutes of intubation was 15.54 (T8). This was statistically significant. The rise of mean SBP in both the groups immediately after intubation was statistically significant but the rise in group N2 was slightly more than group N1 but there after the mean SBP gradually reduced but in group N1 after 10 minutes it reached near baseline value but in group N2 the mean SBP was below the baseline.

Table 3: Systolic blood pressure variation (in mm of Hg).

Drugs/Time	0.1mg Nalbuphine				0.2 mg Nalbuphine			
	No.	Mean	SD	Mean difference[a]	No.	Mean	SD	Mean difference [a]
T0	50	125.74	12.76	-	50	124.22	14.62	-
T1	50	119.82	13.17	5.92	50	116.24	13.15	7.98
T2	50	134.30	18.01	-8.56	50	133.76	21.02	-9.54
T3	50	119.96	17.09	5.78	50	119.10	15.99	5.12
T4	50	116.10	16.83	9.64	50	112.60	16.71	11.62
T5	50	114.16	17.25	11.58	50	112.16	14.06	12.06
T6	50	112.00	14.32	13.74	50	109.56	10.85	14.66
T7	50	111.66	13.27	14.08	50	109.66	11.52	14.56
T8	50	111.36	12.57	14.38	50	108.68	12.56	15.54

'a' denotes Mean difference calculated with basal levels measured at T0, Repeated Measures ANOVA and Factorial ANOVA used, effect of time (F value= 28.3, p<.001), Drugs (F value= 4.5, p= 0.03) and drug*time interaction (F value= 0.12, p = 0.99)Values in bold indicates statistically significant difference, p-value <.05 was significant.

Table 4: Diastolic blood pressure variability (in mm of Hg).

Drugs/Time	0.1mg Nalbuphine				0.2mg Nalbuphine			
	No.	Mean	SD	Mean difference[a]	No.	Mean	SD	Mean difference[a]
T0	50	81.84	10.54	-	50	78.16	11.88	-
T1	50	76.14	11.99	5.70	50	72.24	9.46	5.92
T2	50	83.90	15.82	-2.06	50	82.10	14.99	-3.94
T3	50	76.18	15.68	5.66	50	70.70	12.54	7.46
T4	50	73.58	15.42	8.26	50	66.16	13.06	12.00
T5	50	71.54	17.24	10.30	50	64.90	10.38	13.26
76	50	68.76	15.54	13.08	50	62.72	9.15	15.44
T7	50	79.48	76.40	2.36	50	63.94	9.90	14.22
T8	50	69.92	12.52	11.92	50	64.72	8.88	13.44

'a' denotes Mean difference calculated with basal levels measured at T0;
Repeated Measures ANOVA and Factorial ANOVA used, Effect of time (F value= 6.9, p<0.001), Drugs (F value= 17.8, p<0.001) and drug*time interaction (F value= 0.78, p = 0.61), Values in bold indicates statistically significant difference, p-value <.05 was significant.

Table 4 shows intra group variability of mean diastolic blood pressure (SBP). In group N1, baseline BP was 81.84±10.54, after premedication with study drug at 3 minutes was 76.14±11.99and immediately after induction and intubation was 83.90±15.82.

The mean DBP rise was 2.06 which were statistically insignificant and there after mean DBP at every minute for next 5 minutes gradually reduced with mean DBP reduction of 5.66 (T3), 8.26 (T4), 10.30 (T5), 13.08 (T6), 2.36 (T7) and after 10 minutes after intubation was 11.92 (T8), which was statistically insignificant except at T6. In group N2, the baseline DBP was 78.16±11.88, after premedication with study drug at 3 minutes was 72.24±9.46 and immediately after induction and intubation was 82.10±14.99.

The mean DBP rise was 3.94 which were statistically insignificant. And there after mean DBP at every minute for next 5 minutes gradually reduced with mean DBP reduction of 7.46 (T3), 7.00 (T4), 13.26 (T5), 15.44 (T6), 14.22 (T7) and after 10 minutes after intubation was 13.44 (T8), which was statistically significant from T3-T8. In group N2, the reduction in mean DBP was

statistically significant and the mean DBP continued to reduce during the period of study and end of 10 minutes the DBP was well below the baseline value the reduction was greater than group N1.

Table 5: Mean Arterial Blood Pressure-MAP variability (in mm of Hg).

Drugs/Time	0.1mgNalbuphine				0.2 mg Nalbuphine			
	No	Mean	SD	Mean difference[a]	No.	Mean	SD	Mean difference[a]
T0	50	95.16	11.25		50	91.76	13.09	
T1	50	88.98	10.97	6.18	50	84.58	11.34	7.18
T2	50	99.68	15.67	-4.50	50	99.40	16.42	-7.64
T3	50	89.14	14.76	6.02	50	85.64	14.23	6.12
T4	50	86.84	15.69	8.32	50	81.72	15.76	10.04
T5	50	84.92	15.78	10.20	50	80.70	12.44	11.06
76	50	82.94	14.01	12.22	50	76.98	9.72	14.78
T7	50	82.64	12.91	12.52	50	78.68	10.63	13.08
T8	50	83.22	12.27	11.94	50	77.70	9.76	14.06

'a' denotes Mean difference calculated with basal levels measured at T0, Repeated Measures ANOVA and Factorial ANOVA used, Effect of time (F value= 24.6, p<0.001), Drugs (F value= 20.6, p<.001) and drug*time interaction (F value=0.38, p = 0.92), Values in bold indicates statistically significant difference, p-value <0.05 was significant.

Table 5 shows intra group variability of mean Arterial Blood Pressure (MAP). In group N1, baseline MAP was 95.16±11.25, after premedication with study drug at 3 minutes was 88.98±10.97 and immediately after induction and intubation was 99.68±15.67. The MAP rise was 4.50 which were statistically insignificant and there after MAP at every minute for next 5 minutes gradually reduced with MAP reduction of 6.02 (T3), 8.32 (T4), 10.20 (T5), 12.22 (T6), 12.52 (T7) and after 10 minutes after intubation was 11.94 (T8), which was statistically significant except at T2. In group N2, the baseline MAP was 91.76±13.09, after premedication with study drug at 3 minutes was 84.58±11.34 and immediately after induction and intubation was 99.40±16.42.

The MAP rise was 7.64 which were statistically significant. And there after MAP at every minute for next 5 minutes gradually reduced with MAP reduction of 6.12 (T3), 10.04 (T4), 11.06 (T5), 14.78 (T6), 13.08 (T7) and after 10 minutes after intubation was 14.06 (T8), which was statistically significant from T1-T8.In group N2, the reduction in MAP was statistically significant and the MAP continued to reduce during the period of study and end of 10 minutes the MAP was well below the baseline value the reduction was greater than group N1.

DISCUSSION

Laryngoscopy and intubation following induction of general anesthesia is often associated with tachycardia and hypertension and this is termed as pressor response or hemodynamic response to laryngoscopy and intubation. This response could be detrimental to patients with co-existing diseases such as hypertension, ischemic heart disease, intracranial pathology etc. Hence, various techniques have been tried to attenuate this response. These techniques include increasing the depth of anesthesia with protocol, thiopentone or various inhalational agents or administering various groups of medications such as beta blockers, calcium channel blockers, alpha adrenergic agonists and opioids. Since each class of drugs has their own adverse effects, nalbuphine, an agonist-antagonist opioid has been hypothesized as a safe alternative. In this study, author intend to observe the efficacy of two doses of nalbuphine in attenuating pressor response to laryngoscopy and intubation and also note any adverse effects of the two doses.

In the present study, baseline HR was comparable between the two groups N1 and N2 which was 94.16±16.37 and 92.28±17.10 respectively. The rise in mean HR was seen in both the groups and mean HR rise just after intubation was more in group N2 with 17.88 as compared to group N1 with rise of 15.84, in both the group rise of mean HR was statistically significant and not clinically significant.

Nath R et al, observed that there just after intubation heart rate increased in both the groups with increase more in group N1 than N2, 11.70 versus 3.37 per cent compared to base line but again the increase was not clinically significant in both the groups.[9]

In present study, baseline SBP was comparable between the two groups N1 and N2 which was 125.74±12.76 and 124.22±14.62respectively. Mean SBP increase in both the groups just immediately after intubation (8.56% from baseline and 9.54% from baseline in group N1 and N2 respectively) which was clinically not significant and mean SBP studied over the period of 10 minutes post intubation showed greater drop in mean SBP from T3-T8.

Group N2 showed great control of mean SBP than group N1 throughout the post intubation period. In present study, baseline DBP was comparable between the two groups N1 and N2 which was 81.84±10.54 and 78.16±11.88 respectively. Mean DBP increase in both the groups just immediately after intubation (2.06% from baseline and 3.94% from baseline in group N1 and N2 respectively) which was statistically insignificant. But from T3-T8 the mean DBP continued to decrease well below the baseline value in group N2 and was significant, at the end of 10 minutes there was 13.44% decrease in mean DBP from baseline.

Nath R et al, studied the attenuation of hemodynamic response during laryngoscopy and intubation with low dose Intravenous Nalbuphine comparing two different doses of $0.1mgkg^{-1}$ and $0.2mgkg^{-1}$. Diastolic blood pressure increased in both the groups (N1 and N2) after intubation. In present study, author observed that the mean rise of DBP in group N1 and N2 after intubation was insignificant but thereafter the mean DBP continued to decrease in group N2 from T3-T8 which shows greater stability in group N2, at end of study the DBP drop was significantly low than the baseline showing the hemodynamic stability in group N2.

In present study, baseline MAP was comparable between the two groups N1 and N2 which was 95.16±11.25 and 91.76±13.09 respectively. MAP increased in both the groups just immediately after intubation (4.50% from baseline and 7.64% from baseline in group N1 and N2 respectively) which was statistically significant in group N2 and insignificant in group N1. There after the MAP continued to decrease gradually in both groups from T3-T8 which was statistically significant. By the end of 10 minutes of study the MAP reduction in group N2 was 14.06% as compared to group N1 with 11.94% from the baseline MAP value. Fating DR et al, reported findings similar to present study.[10]

CONCLUSION

Author concluded that nalbuphine in the dose of 0.2mg/kg body weight was more efficacious in attenuating hemodynamic response to laryngoscopy and intubation as compared to 0.1mg/kg dose of Nalbuphine. The incidence of adverse effects was not significant in either of the groups.

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