RESEARCH ARTICLE

COMPARISON OF NALBUPHINE AND DEXMEDETOMIDINE AS AN ADJUVANT TO GENERAL ANAESTHESIA IN EAR SURGERY

Dr. Chirag Ramanlal Patel, *Dr. Ankur Garg, Dr. Parth Shah and Dr. Shashank M.

Resident, B.J. Medical College, Ahmedabad, India

ABSTRACT

Background- As an anesthetic adjuvant, nalbuphine and dexmedetomidine have been shown to provide good perioperative hemodynamic stability with decrease in the intraoperative inhalational agents requirement and also provides adequate postoperative analgesia.

Methods- 60 adult patients of ASA grade I and II were randomly divided into 2 groups of 30 each. Group A received Inj. Nalbuphine 0.3mg/kg i.v.and Group B received Inj. Dexmedetomidine 1 mcg/kg i.v. over 10 minutes, given prior to induction. All patients were observed for baseline pulse rate, SBP and DBP. Thereafter haemoynamic parameters were noted at different time intervals. The RE(response entropy) and SE(state entropy) was maintained between 40 and 60 and also the concentration of sevoflurane required to maintain adequate depth was noted.Postoperative analgesia was assessed by VAS score.

Results- Intraoperatively there was no significant difference in the heart rate, SBP and DBP of patients of both the groups (p- value >0.05). But there was a transient rise in SBP and DBP and fall in heart rate in Group B immediately after administration of study drug. (p- value <0.05). The requirement of sevoflurane concentration was significantly less in Group A as compared to Group B intraoperatively (p>0.05). The mean duration of first rescue analgesia after surgery was 5hours 45 minutes in Group A whereas 2hours 15min in Group B.

Conclusion- Both the drugs as an adjuvant to general an aesthesia attenuate stress response to various noxious stimuli and maintain hemodynamic stability throughout the surgery and decrease the requirement of inhalational agent. Nalbuphine provides better analgesia and reduces requirement of postoperative analgesia as compared to dexmedetomidine. Thus, nalbuphine is more advantageous adjuvant to general anaesthesia.

Citation: Dr. Chirag Ramanlal Patel, Dr. Ankur Garg, Dr. Parth Shah and Dr. Shashank M. 2016. "Comparison of nalbuphine and dexmedetomidine as an adjuvant to general anaesthesia in ear surgery", *International Journal of Current Research*, 8, (04), 29807-29813.

INTRODUCTION

Many drugs like clonidine, dexmedetomidine, nalbuphine, etc. have been studied as an adjuvant to general anaesthesia for haemodynamically stability during laryngoscopy and intraoperative period as well as postoperative analgesia for better patient outcome (Mondal, 2014). Laryngoscopy and orotracheal intubation is associated with haemodynamic response and a rise in plasma concentrations of catecholamine like noradrenaline, adrenaline and dopamine. The hemodynamic response to laryngoscopy and intubation was described in 1940 by Reid and Brace (Reid, 1940). Rise in sympathetic hormones during intubation is associated with complications in high risk patients which can increase

morbidity as well as mortality in some patients (Fox, 1977 and Derbyshire, 1983). Nalbuphine is an agonist antagonist opioid acting on µ receptors as antagonist and ê receptor as agonist with analgesic potency equal to morphine and its antagonistic potency is approximately 1/4th that of nalorphine. Its cardiovascular stability, longer duration of analgesia, no respiratory depression, less nausea and vomiting and potential safety in over dosage makes it an ideal analgesic for use in balanced anaesthesia (Klepper *et al.*, 1986 and Lake *et al.*, 1984). α-2 adrenergic agonists decrease sympathetic tone and pre-operative use of clonidine, an α-2 adrenergic agonist has been shown to blunt the hemodynamic responses to noxious stimulation and to prevent the overall hemodynamic variability (Keniya *et al.*, 2011). Dexmedetomidine, a more specific and selective α-2 adrenergic agonist than clonidine has a shorter duration of action than clonidine (Wijeysundera *et al.*, 2003) and because of its sedative and analgesic properties it also can be used as an adjunct to general anesthetics.

*Corresponding author: Ankur Garg,
Resident, B.J. Medical College, Ahmedabad, India.

Aims and Objectives

The aims of our comparative study between two adjuvants, injection nalbuphine and inj. Dexmedetomidine were, to observe the effects of these drugs on haemodynamic response during laryngoscopy, intraoperative vitals, depth of anaesthesia, intra and postoperative analgesia and any significant side effect and complication.

Procedure

After institute's ethical committee approval & obtaining an informed consent, 60 patients were included in a randomized prospective controlled study from January 2015 to October 2015 at B.J.M.C., Ahmedabad.

Inclusion criteria

- Age group 18years to 60years.
- Patients with ASA status I and II.

Exclusion criteria

- Unwilling to give consent.
- History of allergy to drugs.
- Patients predicted with difficult intubation, prolonged laryngoscopic time (>30 seconds).
- Patients with hypertension, cardiac, coronary, renal, hepatic, cerebral diseases and vascular diseases.
- Pregnant woman.

All the patients were assessed a day before surgery. Routine investigations were done. Airway assessment was done by mallampati gradation and mallampati grade 1 and II patients were selected for the study. 60 adult patients considered for study were divided into 2 groups of 30 members each randomly.

- Group A received Inj. Nalbuphine 0.3 mg/kg i.v.over 10 minutes.
- Group B received Inj. Dexmedetomidine 1mcg/kg i.v.over 10 minutes.

After taking the baseline pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), ECG, EtCO2& SPO2, a wide bore IV line was secured & infusion of DNS was started. Study drug was given 3 minutes prior to intubation in Group A and 10 minutes prior to intubation in Group B. Patients were premedicated with Inj. Ondansetron 0.15mg/kg i.v.and Inj. Glycopyrolate 4 microgram/kg i.v. All patients were pre-oxygenated with 100% oxygen for 3-5 minutes. Induction was done with injPropofol 2mg/kg and inj Succinylcholine 2mg/kg intravenously after pre-oxygenation. In both the groups intubation and laryngoscopy was performed within a period of 20 seconds. After checking the position the endotracheal tube was fixed. Anaesthesia was maintained with O_2 (49%), N_2O (49%) and Sevoflurane (1-2%) and muscle relaxation was done with Injatracurium 0.5 mg/kg i.v. bolus dose followed by intermittent doses. All patients were observed for pulse rate, systolic blood pressure, diastolic blood pressure, entropy, EtCO2 & SPO2 after injecting the drug, on

intubation and 1 minute, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 60 minutes,90 minutes, 120 minutes after intubation and also immediately after extubation. The depth of anaesthesia was evaluated by entropy [State entropy (SE) and response entropy (RE)]analysis (Datex – Ohmeda S/5 Avanceworkstation^{TM}workstation, GE Healthcare, Helsinki, Finland. The RE and SE was maintained between 40 and 60 and also the concentration of sevoflurane required to maintain adequate depth was noted. At the end of surgery, patients were reversed using inj. Neostigmine 0.05mg/kg and inj. Glycopyrrolate 0.008 mg/kg, and extubated when patients were fully conscious with normal tone and power. Patients were shifted to anaesthetic recovery room and monitored for complications like nausea, vomiting, respiratory depression, hypotension, hypertension, tachycardia, bradycardia and drowsiness. Patients were followed up for 12 hours. Postoperative analgesia was graded with VAS score. Time for rescue analgesia was noted. Rescue analgesia was given when patient had VAS score $\geq$ 4.

Statistical Analysis

Data was expressed as mean values ± standard deviation (SD). Quantitative data was analyzed using t-test and qualitative by chi square test using. Statistical calculations were carried out using Microsoft Office Excel 2010 and Graph Pad Prism 6.05 (quickcalc) Software. Changes in hemodynamic variables from baseline and a comparison of means were analyzed by paired t-test for each time interval. A p-value < 0.05 was considered to be statistically significant.

RESULTS

There was no significant difference amongst the groups with regard to demographic variables ($P > 0.05$) (Table 1). There was a fall in heart rate in patients of Group B immediately after administration of study drug, but, intraoperatively there was no significant difference in the heart rate of both the groups (p-value >0.05). (Table 2, Figure 1).

There was a rise in SBP and DBP in patients of Group B immediately after administration of study drug. But, intraoperatively there was no significant difference in SBP and DBP of both the groups (p- value >0.05).

(Table 3,4 and Figure 2,3) The depth of anaesthesia assessed by RE and SE was comparable between two groups at all time points during maintenance period (p>0.05). Postopaeratively VAS score was noted for all the patients. Patients in Group A required rescue analgesia later as compared to Group B patients (Figure 4).

The FI sevoflurane concentration was significantly less in Group A as compared to Group B intraoperatively (p<0.05). (Figure 5)

Duration of first rescue analgesia after surgery

Group A- 5hours 45min (mean)

Group B- 2 hours 15min (mean)

Table 1. Demographic characteristics

S.No.	Patient characteristics	GROUP A (Mean ± S.D.)	GROUP B (Mean ± S.D.)	p-VALUE
1.	Age (years)	38.9 ± 14.6	39.7 ± 11.4	0.81
2.	Gender (male/female)	17/13	15/15	0.343
3.	Weight (kg)	60.8 ± 11.6	59.6 ± 9.87	0.66
4.	ASA I/II	17/13	16/14	0.343
5.	Duration of surgery (min)	138.9 ± 11.8	140.9 ± 13.7	0.54
6.	Type of surgery			
	A)Mastoidectomy	17	13	
	B)Tympaoplasty	14	16	

Table 2. Changes in HR intraoperatively

S.No.	Time	GROUP A (Mean ± S.D.)	GROUP B (Mean ± S.D.)	p- value
1	Baseline	98.23 ± 9.89	97.23 ± 10.76	0.70
2	After medication	99.9 ± 8.43	92.43 ± 9.76	0.002
3	On intubation	101.1 ± 9.54	103.54 ± 10.54	0.35
4	1min after intubation	94.86 ± 8.45	98.56 ± 9.34	0.11
5	5min after intubation	92.56 ± 10.37	94.86 ± 9.46	0.37
6	10min after intubation	90.53 ± 9.28	89.54 ± 10.47	0.69
7	15min after intubation	90.16 ± 10.74	88.76 ± 9.27	0.59
8	30min after intubation	90.56 ± 9.76	92.76 ± 10.56	0.40
9	60min after intubation	89.8 ± 8.56	90.54 ± 9.45	0.75
10	90min after intubation	88.3 ± 11.46	83.96 ± 10.35	0.12
11	120min after intubation	85.3 ± 9.95	85.83 ± 8.75	0.82
12	Post Extubation	94.06 ± 10.26	96.13 ± 9.46	0.41

Table 3. Changes in Systolic B.P. intraoperatively

S.No.	Time	GROUP A (Mean ± S.D.)	GROUP B (Mean ± S.D.)	p- value
1	Baseline	139.16 ± 8.45	143.36 ± 15.2	0.18
2	After medication	130.56 ± 9.41	153.83 ± 16.18	<0.0001
3	On intubation	128.93 ± 12.85	135.46 ± 15.89	0.08
4	1min after intubation	121.96 ± 12.18	128.3 ± 15.67	0.08
5	5min after intubation	119.7 ± 8.98	120.66 ± 14.18	0.76
6	10min after intubation	118.13 ± 11.63	121.26 ± 16.79	0.46
7	15min after intubation	117.7 ± 11.51	116.2 ± 16.79	0.68
8	30min after intubation	117.86 ± 13.51	114.26 ± 15.98	0.36
9	60min after intubation	117.1 ± 12.84	113.8 ± 14.76	0.35
10	90min after intubation	120.86 ± 12.96	113.9 ± 13.88	0.04
11	120min after intubation	122.03 ± 11.92	113.9 ± 13.91	0.02
12	Post Extubation	131.33 ± 10.06	124.13 ± 12.42	0.01

Table 4. Changes in diastolic B.P. intraoperatively

S.No.	Time	GROUP A (Mean ± S.D.)	GROUP B (Mean ± S.D.)	p- value
1	Baseline	87.33 ± 9.67	86.67 ± 8.32	0.77
2	After medication	86.23 ± 10.36	94.26 ± 7.73	0.001
3	On intubation	87.45 ± 11.73	89.35 ± 8.63	0.47
4	1min after intubation	83.56 ± 8.75	84.89 ± 10.73	0.60
5	5min after intubation	85.23 ± 8.65	84.26 ± 9.64	0.68
6	10min after intubation	84.83 ± 9.45	85.48 ± 10.63	0.80
7	15min after intubation	86.43 ± 10.26	87.54 ± 8.63	0.65
8	30min after intubation	87.13 ± 11.63	86.58 ± 11.72	0.85
9	60min after intubation	87.42 ± 10.72	88.43 ± 10.63	0.71
10	90min after intubation	86.46 ± 9.36	89.73 ± 9.63	0.18
11	120min after intubation	84.56 ± 8.63	89.65 ± 8.46	0.02
12	Post Extubation	91.13 ± 9.46	94.92 ± 10.73	0.15

DISCUSSION

Nalbuphine is a kappa agonist mu antagonist with cardiovascular stability (Miller *et al.*, 1980), lesser potential for respiratory depression (Romagnoli *et al.*, 1980), onset of action between 2 -3 minutes, duration of action 3 to 6 hours with minimal side effects in dose of 0.2 mg/kg (Priti *et al.*, 2010). Dexmedetomidine is a central sympatholytic and as a peripheral ganglionic blocker. This action is predominantly performed through agonistic action at the pre-synaptic alpha 2 adrenergic receptors. It has high ratio of specificity for alpha 2 receptor than alpha 1 receptor i.e. 1600: 1. Dexmedetomidine causes a decrease in the release of catecholamines (both epinephrine and norepinephrine) in the synaptic junction (McCallum, 1998). Transient hypertensive response has been observed with higher doses (1–4 mcg/kg).
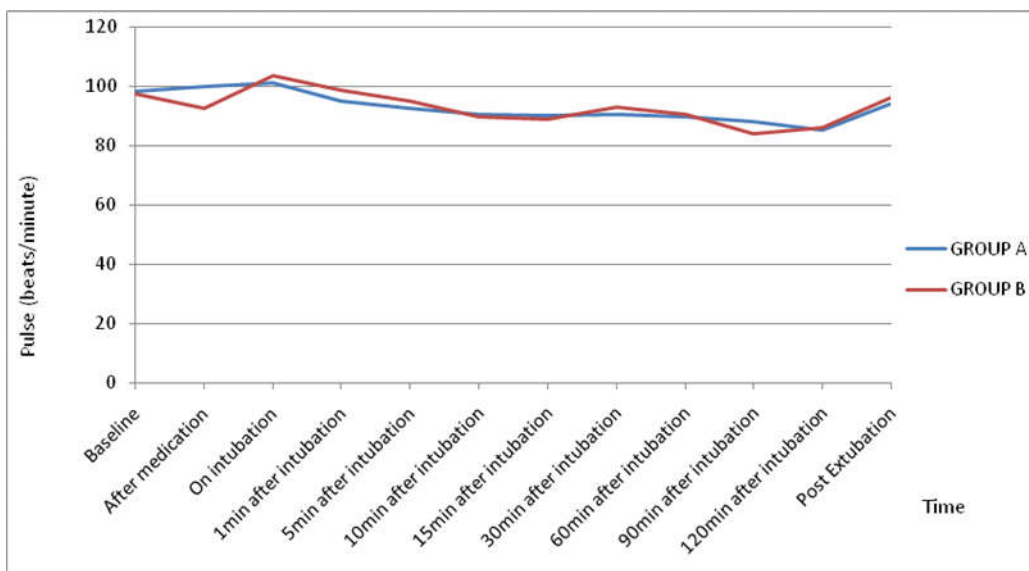
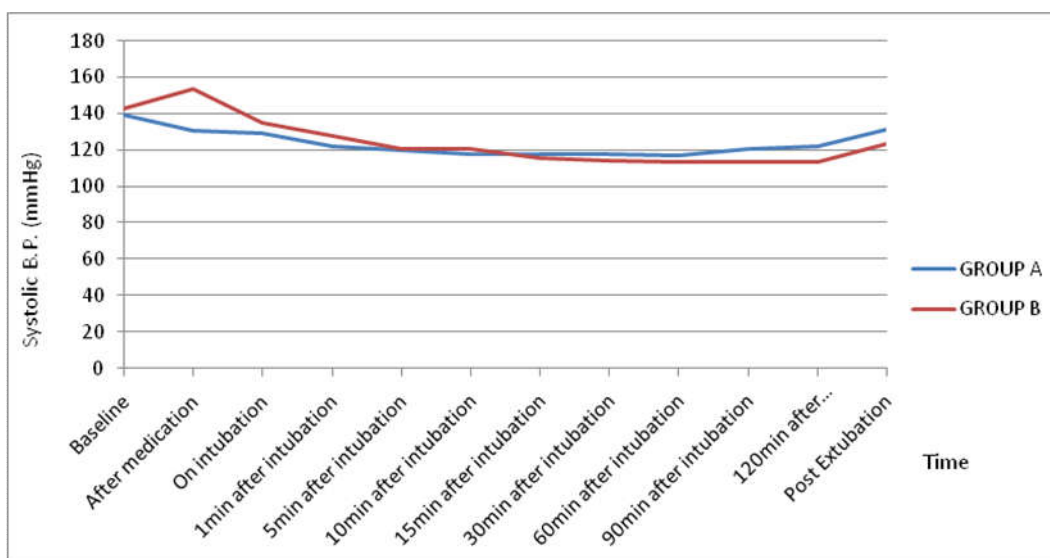**Figure 1. Changes in HR at various times intraoperatively**

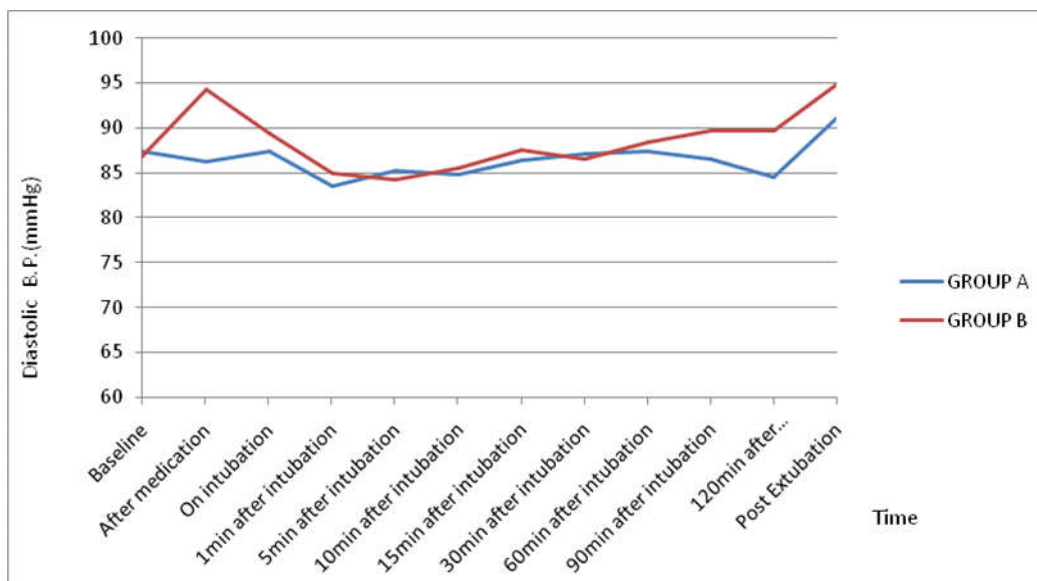**Figure 2. Changes in SBP (Systolic B.P.) at various times intraoperatively**

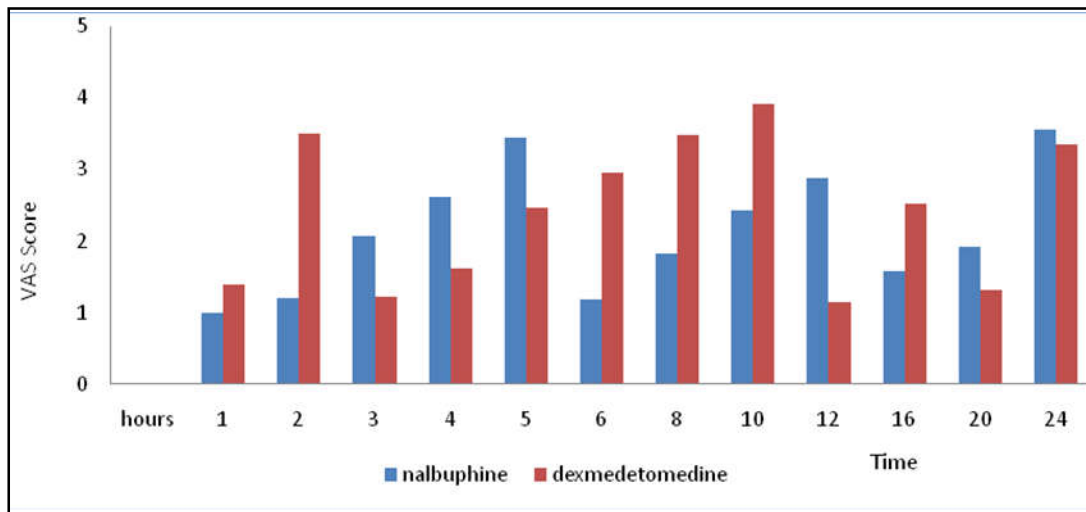**Figure 3. Changes in Diastolic B.P. (DBP) at various times intraoperatively**
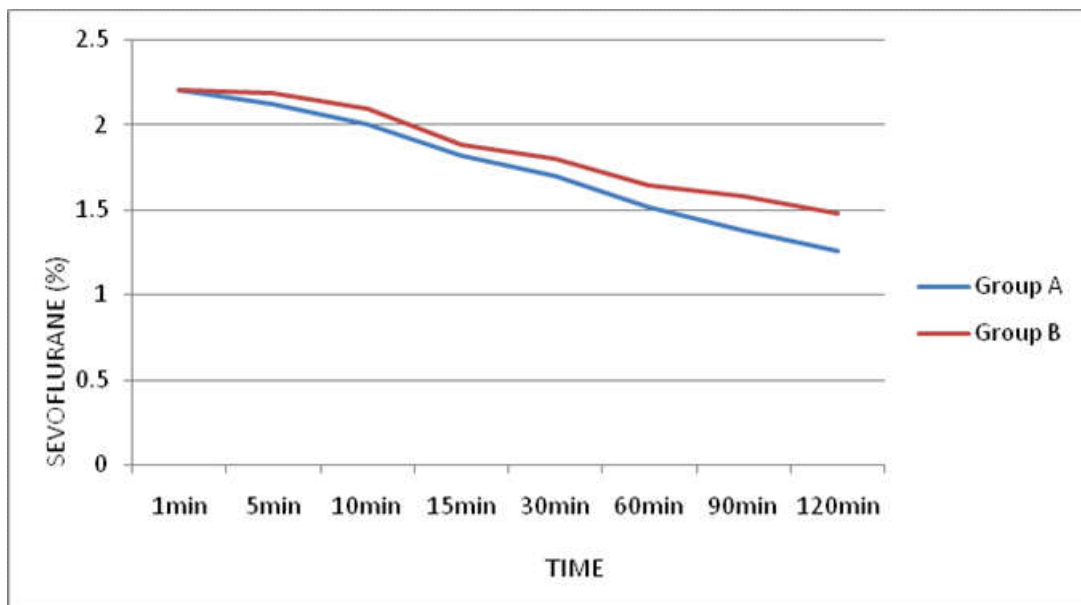
Figure 4. Postoperative VAS Score

Figure 5. Intraoperative requirement of sevoflurane

This is attributed to initial stimulation of α-2B receptors present in vascular smooth muscles. This hypertensive episode settles once there is decrease in central sympathetic outflow (Sudheesh *et al*., 2011). Similar response was seen in our study also. Lawrence and De Lange found that a single dose of 2μg/kg of dexmedetomidine before induction of anesthesia attenuated the hemodynamic response to intubation as well as that to extubation (Lawrence *et al*., 1997). Chawda *et al* studied 60 patients for elective laparoscopy surgery to receive either saline or Nalbuphine 0.2mg/kg. Nalbuphine 0.2 mg/kg prevented a marked rise in heart rate and mean arterial pressure associated with laryngoscopy and orotracheal intubation (Chawda *et al*., 2010). Ahsan *et al* compared nalbuphine 0.2mg/kg with placebo.

They noticed increases in HR and MAP just after induction, which was significant i.e. more than 20% rise from baseline in placebo group. Nalbuphine prevented this rise which was

similar as in our study (Bekker *et al*., 2008) In our study also, the stress response was attenuated with both the study drugs during intubation. Bekker *et al*., who reported that dexmedetomidine, given at a similar dose, was effective in blunting the increase in systolic BP perioperatively (Bekker *et al*., 2008). Hogue *et al*. reported that dexmedetomidine preserves baroreflex sensitivity, and that patient had a normal HR response to BP. They noted slowing of the HR is mostly from sympathetic withdrawal and not due to enhanced vagal activity (Hogue *et al*., 2002). The highest density of α2 receptors has been detected in the locus ceruleus, the predominant noradrenergic nucleus in the brain and an important modulator of vigilance. The sedative effects of α2 adrenoceptor activation have been attributed to this site in the CNS, and this allows psychomotor function to be preserved while making the patient rest comfortably, so patients are able to return to their baseline level of consciousness when stimulated (Kamibayashi *et al*., 2000) Dexmedetomidine also

shows ability to attenuate stress responses during surgery due to its sympatholytic properties (Talke *et al.*, 2000). We found that nalbuphine has similar potency as dexmedetomidine in maintaining the hemodynamic stability intraoperatively. Use of haemodynamic end points for assessing the depth of anaesthesia in a study on sympatholytic drugs such as dexmedetomidine would be unreliable as there may be compromise in the depth of anaesthesia. Several electroencephalogram-dependent indices such as bispectral index and entropy have been used to measure the depth of anesthesia (Ellerkmann *et al.*, 2004) Entropy is a useful monitor for measuring the electroencephalographic effects of increasing and decreasing sevoflurane concentration and assessing the depth of anesthesia (White *et al.*, 2006 and Magalhães *et al.*, 2004). Analogous to the bispectral index, entropy displays a high degree of specificity and sensitivity in assessing consciousness during anesthesia. Using bispectral index to assess the depth of anesthesia, Magalhães *et al.* showed decreased requirement of sevoflurane with continuous infusion of dexmedetomidine during general anesthesia. In our study, we used entropy to measure the depth of anesthesia, thereby eliminating the bias of evaluation by hemodynamic parameters as in earlier studies (Magalhães *et al.*, 2004).

In our study, adequate depth of anaesthesia was maintained throughout surgery with response and state entropy being maintained between 40 and 60 in both the drugs.We observed that requirement of inhalational agent was reduced in both the groups. The analgesic potency of nalbuphine is equivalent to that of morphine on a milligram basis. Yeh *et al* in a study using different combinations of morphine and nalbuphine found no difference in patient controlled analgesia requirements in postoperative period in patients undergoing open gynecological surgeries (Yeh *et al.*, 2008). Minai and Khan reported that the need for supplemental analgesia was lower with patients in nalbuphine group (Minai and Khan, 2003). Dexmedetomidine has sedative and analgesic properties, its safety and efficacy has been widely proven in multiple procedures (Mato *et al.*, 2002). Jaakola *et al.* evaluated analgesia after systemic administration of different doses of dexmedetomidine and fentanyl and found that dexmedetomidine had a moderate analgesic effect that was maximized at 0.5 mcg/kg (Jaakola *et al.*, 1992). In patients undergoing laparoscopic tubal ligation, a 33% decrease in morphine use post-operatively was observed when dexmedetomidine was used at a dose of 0.4 mcg/ kg (Aho *et al.*, 1991). The need for rescue analgesia was significantly less in nalbuphine group. Hence, post operative analgesia was found to be better with nalbuphine group in our study. Lake *et al.* have reported less cardiac depression with Nalbuphine in comparison to morphine, even when the former is used in high doses (3mg/kg) in cardiac surgeries (Lake *et al.*, 1982). Nalbuphine has the advantage of cardiovascular stability and rapid recovery (Zaigmond *et al.*, 1987). Respiratory depression caused by nalbuphine has a ceiling effect at higher doses unlike morphine and other opioids (Gal *et al.*, 1982). With dexmedetomidine, hypotension and bradycardia may occur with ongoing therapy mediated by central α 2A-AR, causing decreased release of noradrenaline from the sympathetic nervous system. Long-term use of dexmedetomidine leads to super sensitization and upregulation of receptors; so, with

abrupt discontinuation, a withdrawal syndrome of nervousness, agitation, headaches, and hypertensive crisis can occur (Morgan *et al.*, 2006). In dexmedetomidine group, 2 patients had bradycardia in for which inj. Atropine 0.6mg i.v.was given and 5 patients had nausea and vomiting. In nalbuphine group, 4 patients had respiratory depression which was corrected by oxygen supplementation and 7 patients had nausea and vomiting.

Conclusion

In conclusion, both the drugs as an adjuvant to general anaesthesia attenuate stress response to various noxious stimuli and maintain hemodynamic stability throughout the surgery and decrease the requirement of inhalational agent. However, nalbuphine provides better analgesia and reduces requirement of postoperative analgesia as compared to dexmedetomidine. Thus, nalbuphine is more advantageous adjuvant to general anaesthesia in comparison with dexmedetomidine.

REFERENCES

Aho, M.S., Erkola, O.A., Scheinn, H., Lehtinen, A.M., Korttila, K.T. 1991. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *AnesthAnalg.*, 73:112-8.

Ahsan, M., Etizaz, H.K., Zahid, A.R.N. 2005. Nalbuphine prevents haemodynamic response to endotracheal intubation. *J Coll Physicians Surg Pak.*, 15:668-70.

Bekker, A., Sturaitis, M., Bloom, M., Moric, M., Golfinos, J., Parker, E., *et al.* 2008. The effect of dexmedetomidine on perioperative hemodynamics in patients undergoing craniotomy. *AnesthAnal.,* 107:1340-7.

Bloor, B.C., Flacke, W.E. 1982. Reduction of halothane anesthetic requirements by clonidine, an a- 2 -adrenergic agonist. *AnestAnalg.*, 61:741-5.

Chawda, P.M., Pareek, M.K., Mehta, K.D. 2010. Effect of nalbuphine on haemodynamic response to orotracheal intubation. *J AnaesthClinPharmacol.*, 26:458-60

Derbyshire, D.R., Chmielawski, A., Fell, D., Vater, M., Achola, K., Smith, G. 1983. Plasma catecholamine responses to tracheal intubation. *AnesthAnalg.*, 55:855-60.

Ellerkmann, R.K., Liermann, V.M., Alves, T.M., Wenningmann, I, Kreuer, S., Wilhelm, W., *et al.* 2004. Spectral entropy and bispectral index as measures of the electroencephalographic effects of sevoflurane. *Anesthesiology*, 101:1275-82.

Fox, E.J., Sklar, G.S., Hill, C.H., Villanueva, R., King, B.D. 1977. Complications related to the pressor response to endotracheal intubation. *Anesthesiology*, 1977;44:524-5.

Gal, T.J., DiFazio, C.A., Moscicki, J. 1982. Analgesic and respiratory depressant activity of nalbuphine: a comparison with morphine. *Anesthesiology,* 57:367-74.

Hogue, C.W. Jr, Talke, P., Stein, P.K., Richardson, C., Domitrovich, P.P., Sessler, D.I. 2002. Autonomic nervous system responses during sedative infusions of dexmedetomidine. *Anesthesiology*, 97:592-8

Jaakola, M.L., Ali-Melkkilä, T., Kanto, J., Kallio, A., Scheinin, H., Scheinin, M. 1992. Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. *Br J Anaesth.,* 68:570-5.

Kamibayashi, T., Maze. M. 2000. Clinical uses of alpha-2 adrenergic agonists. *Anesthesiology*, 93 :1345–9.

Keniya, V.M., Ladi, S., Naphade, R. 2011. Dexmedotomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. *Indian J Anaesth.,* 55:352-7.

Klepper, I.D., Rosen, M., Vickers, M.D., Mapleson, W.W. 1986. Respiratory function following nalbuphine and morphine in anaesthetized man. *Br J Anaesth.*, 58:625-9.

Lake, C.L., Duckworth, E.N. and DiFazio, C.A. 1982. Cardiovascular effects of nalbuphine in patients with coronary or valvular heart disease. Anesthesiology. 57(6);498-503.

Lake, C.L., Duckworth, E.N., Difazio, C.A., Magruder, M.R. 1984. Cardiorespiratory effects of nalbuphine and morphine premedication in adult cardiac surgical patients. *ActaAnaesthesiolScand.*, 28:305-9.

Lawrence, C.J., De Lange, S. 1997. Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and perioperative haemodynamic stability. *Anesthesia*, 52: 736-44.

Magalhães, E., Govêia, C.S., Ladeira, L.C., Espíndola, B.V. 2004. Relationship between dexmedetomidine continuous infusion and end-tidal sevoflurane concentration, monitored by bispectral analysis. *Rev Bras Anestesiol.,* 54:303–10.

Mato, M., perez, a, otero, J, torresl, M. 2002. Dexmedetomidine, a promising drug. *Rev EspAnestesiol Reanim.*, 49:407-20.

McCallum, J.B., Boban, N., Hogan, Q., Schmeling, W.T., Kampine, J.P., Bosnjak, Z.J. 1998. The mechanism of alpha2-adrenergic inhibition of sympathetic ganglionic transmission. *AnesthAnalg.*, 87:503–10.

Miller, R.R. 1980. Evaluation of nalbuphine hydrochloride. *Am J Hosp Pharma.*, Jul;37(7):942-9

Minai, F. N. and Khan, F. A. 2003. A comparison of morphine and Nalbuphine for intraoperative and postoperative analgesia. *Journal of the Pakistan Medical Association*, 53(9):391-6.

Mondal, S., Mondal, H., Sarkar, R., Rahaman, M. 2014. Comparison of dexmedetomidine and clonidine for attenuation of sympathoadrenal responses and anesthetic requirements to laryngoscopy and endotracheal intubation. *Int J Basic ClinPharmacol.*, 2014; 3(3): 501-6.

Morgan, G.E., Mikhail, M.S., Murray, M.J. 2006. Preoperative Medication in Clinical Anaethesia. Morgan GE, Mikhail MS, Murray MJ, Editors. 4 th ed. New York: Mcgraw Hill.

Priti, M. Chawda, Mayuresh K. Pareek, Ketan D Mehta. 2010. Effect of Nalbuphine on Haemodynamic Response to Orotracheal Intubation. *J Anaesth Clin Pharmacol.*, 26(4):458-60.

Reid, L.C., Brace, D.E. 1940. Irritation of the respiratory tract and its reflex ef¬fect upon heart. *SurgGynaecObstet.*, 70:157-62.

Romagnoli, A., Keats, A.S. 1980. Ceiling effect for respiratory depression by nalbuphine. clinpharmacolther. 1980 Apr; 27(4):478-85.

Sudheesh, K., Harsoor, S. 2011. Dexmedetomidine in anaesthesiapractice: A wonder drug? *Indian Journal of Anaesthesia.,* 55(4):323-324.

Talke, P., Chen, R., Thomas, B., Aggarwall, A., Gottlieb, A., Thorborg, p, heard s, Cheung a, son sl, Kallio a: 2000. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *AnesthAnalg.*, 90:834-9.

White, P.F., Tang, J., Romero, G.F., Wender, R.H., Naruse, R., Sloninsky, A., *et al*. 2006. A comparison of state and response entropy versus bispectral index values during the perioperative period. *AnesthAnalg,* 102:160-7.

Wijeysundera, D.N., Naik, J.S., Beattie, W.S. 2003. a-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta analysis. *Am J Med.,* 114:742-52.

Yeh, Y.C., Lin, T. F., Lin, F.S., Wang, Y.P., Lin, C.J. and Sun, W.Z. 2008. Combination of opioid agonist and agonist-antagonist: patient-controlled analgesia requirement and adverse events among different-ratio morphine and nalbuphine admixtures for postoperative pain. *British Journal of Anaesthesia*, 101(4):542-8.

Zaigmond, E.K., Winime, A.P., Raza, S.M.A., *et al*. 1987. Nalbuphine as an analgesic component in balanced anesthesia for cardiac surgery. *Anesth. Analg*. 66:1155-64.

****