(Acta Anaesth. Belg., 2021, 72, 1-6)

Intranasal dexmedetomidine for attenuation of hemodynamic response to laryngoscopy and intubation in adults

A. Kochhar (*), P. Panjiar (**), K. Mohd Butt (**)

Abstract : *Background :* To evaluate effectiveness of intranasal dexmedetomidine for attenuation of hemodynamic response to laryngoscopy and intubation in adults.
Design and setting : This prospective randomized study included 90 American Society of Anesthesiologists (ASA) status I, adult patients of either sex, aged between 18-60 years, and undergoing elective surgery under general anesthesia requiring endotracheal intubation.
Methods : Patients were randomly assigned to one of three groups of 30 each, to receive either intranasal saline (Group C), intranasal dexmedetomidine 1µg/kg (Group D_1) or intranasal dexmedetomidine 2µg/kg (Group D_2), administered 30 minutes before the induction of anesthesia. Anesthesia technique was standardized for all patients taking part in the study.
Main outcome measures : Primary outcome studied was attenuation of hemodynamic response to laryngoscopy and intubation. Secondary parameters studied were sedation score and dose of propofol required at induction.
Results : There was a statistically significant rise in heart rate and systolic, diastolic and mean arterial pressures at 1, 3, and 5 minutes of intubation in group C as compared to groups D_1 and D_2. Sedation score was significantly higher in groups D_1 and D_2 ($p<0.0001$). Propofol requirement was significantly lower in groups D_1 and D_2 ($p<0.0001$). Intranasal dexmedetomidine 2µg/kg was associated with higher a incidence of bradycardia.
Conclusion : Intranasal dexmedetomidine (1µg/kg and 2µg/kg) effectively diminishes hemodynamic changes associated with laryngoscopy and intubation in adult patients undergoing elective surgery. Intranasal dexmedetomidine 2µg/kg is associated with significant bradycardia. Intranasal dexmedetomidine also provides effective preoperative sedation and decreases the dose of propofol required for induction of anesthesia.

Keywords : dexmedetomidine ; hemodynamic response ; intranasal ; laryngoscopy.

Introduction

The catecholamines released during laryngoscopy and intubation, as a result of reflex sympathetic stimulation, cause in tachycardia and hypertension. This cardiovascular stress response can be deleterious in susceptible patients and may lead to arrhythmias, myocardial ischemia and stroke (1).

Dexmedetomidine is an alpha-2 agonist that produces sedation, anxiolysis, analgesia and sympatholysis. The various routes of administration of dexmedetomidine include intravenous, intramuscular, intranasal and sublingual (2).

Intravenous dexmedetomidine when given as an infusion over 10-15 minutes in the operating room before induction, has been shown to blunt hemodynamic response to laryngoscopy and intubation in adults (3, 4). However, hypotension and bradycardia has also been reported (5).

Intranasal dexmedetomidine administration provides more gradual onset as compared to the intravenous route. It is well accepted as it is tasteless and non-irritant (2). The median time for onset of sedation is 25 minutes (6) and peak effect occurs at 45 minutes. Bioavailability is 40-65% (7,8).

A recent study by Jayaraman et al. in morbid obese adults shows that intranasal dexmedetomidine (1µg/kg) given as premedication 45 minutes before surgery, provides sedation, anxiolysis and

Anjali Kochhar, MD ; Pratibha Panjiar, DA, DNB ; Khairat Mohd Butt, MD
(*) Department of Anaesthesia, Critical Care and Pain Medicine, VMMC and Safdarjung Hospital, New Delhi, India ; Past affiliation : Department of Anaesthesiology, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, New Delhi, India.
(**) Department of Anaesthesiology, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, New Delhi, India.
Corresponding author : Dr Anjali Kochhar, Department of Anaesthesia, Critical Care and Pain Medicine, VMMC and Safdarjung Hospital, New Delhi, India (110029), 262, Narmda Apartments, Alaknanda, New Delhi, India. Phone : +91 9999197721.
Email : kochharanjali0@gmail.com

Paper submitted on August 16, 2020 and accepted on March 2, 2021.
Conflict of interest : None
Ethical clearance by Institutional ethics committee Jamia Hamdard, New Delhi.
Trail registered with clinical tral regisrty of India (CTRI) : CTRI/2017/07/009180.
Informed consent obtained from all the patients.

incomplete blunting of hemodynamic response to noxious stimuli such as laryngoscopy and intubation (9).

In children undergoing adenotonsillectomy, intranasal dexmedetomidine 2 µg/kg administered 30 minutes before anesthesia induction was found to be effective in blunting hemodynamic response (MAP and HR) to laryngoscopy and intubation (10).

In addition to morbid obese and pediatric patients, intranasal dexmedetomidine can be given to adults when oral premedication is not feasible. Our hypothesis is that intranasal dexmedetomidine in adults could provide a sedated, tranquil patient ready for induction when wheeled in the operation theatre, and that intranasal dexmedetomidine could blunt hemodynamic response to laryngoscopy and intubation.

Therefore, we planned a study to evaluate intranasal dexmedetomidine as premedication and for attenuation of hemodynamic response to laryngoscopy and intubation in healthy adults undergoing elective surgery.

Methods

This double-blind, randomized study was conducted after obtaining approval from the institutional ethics committee and after registration with the clinical trial registry of India (CTRI/2017/07/009180). Written informed consent was obtained from all the patients.

This study included 90 American Society of Anesthesiologists (ASA) status I, adult patients of either sex, aged between 18-60 years, undergoing elective surgery under general anesthesia and requiring endotracheal intubation. Patients having any nasal pathology, history of allergy to the drug used, difficult airway and pregnancy were excluded from the study.

Patients meeting the inclusion criteria during the pre-anesthetic evaluation were randomly assigned into three groups of 30 each with the help of a computer generated table of random numbers. Group C received intranasal saline (2 mL). Group D_1 received intranasal dexmedetomidine (1 µg/kg), diluted in 2 mL saline and Group D_2 received intranasal dexmedetomidine (2 µg/kg) diluted in 2 mL saline. All patients were given a tablet alprazolam 0.25 mg orally, in the morning of surgery as standardized protocol.

All the drugs were prepared by an anesthesiologist, who did the coding and was not involved in either administration of drugs or data collection. All the medications were administered by an anesthesia nurse who was not involved in the study. Drugs were given by nasal instillation, diluted in 2 mL, 30 minutes before the induction of anesthesia. The dose of the dexmedetomidine was adapted to nearest weight of the patient. Both patient and nurse were blinded to group allocation.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), respiratory rate and oxygen saturation were recorded at baseline and 30 minutes after premedication. Sedation score (Ramsay Sedation Score) was also recorded before and 30 minutes after premedication (11). Any occurrence of respiratory depression, defined as ventilatory frequency < 8 bpm and/or oxygen saturation < 93% without oxygen supplementation, was also recorded.

Anesthesia technique was standardized in all the three groups. Electrocardiogram, noninvasive blood pressure, oxygen saturation, end-tidal carbon dioxide ($EtCO_2$) and minimum alveolar concentration (MAC) were monitored in all patients. Ringer's lactate was started after securing an intravenous (i.v.) line. Anesthesia was induced with i.v. fentanyl 2 µg/kg and i.v. propofol titrated until loss of verbal response. Endotracheal intubation was facilitated by vecuronium 0.08 mg/kg. Bag and mask ventilation was done using oxygen in nitrous oxide (50:50) and sevoflurane (2 vol%) at a flow rate of 8 L/min. Laryngoscopy was attempted by a single experienced anesthesiologist 3 minutes after the administration of vecuronium. Duration of laryngoscopy was timed and all parameters were recorded by an anesthesiologists blinded to group allocation.

Decoding was done at the end of study. Primary outcome studied was attenuation of hemodynamic response to laryngoscopy and intubation for which hemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure) were recorded at baseline (pre-operative period before administration of study drugs) and at 1, 3 and 5 minutes of laryngoscopy and intubation. The amount of propofol required for induction was also recorded.

Any episode of bradycardia (HR <60 bpm) and hypotension (30% fall in SBP) were recorded and subsequently treated with atropine 0.5 mg i.v. and mephentermine 3 mg i.v. bolus, respectively.

Statistical analysis

Sample size calculation was done based on pilot cases data. Taking a mean difference of 7.6 with standard deviation of 9.1 in the mean heart rate at 3 minutes, a sample size of 26 was estimated with

90% power. A sample size of 30 patients in each group was taken to account for non-response. Cases with duration of laryngoscopy >15 seconds were excluded from analysis.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation (SD). Quantitative variables were compared using one way analysis of variance (ANOVA). Paired t-test was used for comparison across follow up within the groups. Qualitative variables were correlated using Chi-Square test. A p value of <0.05 was considered statistically significant. The data was entered in Microsoft excel (MS EXCEL) spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

The demographic profile of patients, MAC value at the time of laryngoscopy and the time required for laryngoscopy were comparable in all three groups (Table 1).

There was no significant difference in the baseline HR between the groups. After induction, a decrease in HR was observed in all the groups. In group C, there was increase in HR from the baseline at 1 and 3 minutes following intubation. HR returned to baseline values at 5 minutes post intubation. In group D_1 and group D_2 there was a decrease in HR compared to the baseline at 1, 3, and 5 minutes following intubation. The difference in the HR between group C and group D_1 and group D_2 was found to be statistically significant post induction and at 1, 3 and 5 minutes of intubation ($p<0.0001$ at all time points) as shown in Table 2.

There was no significant difference in the baseline SBP, DBP, MAP between the groups.

Table 1

Demographic profile, MAC and Laryngoscopy time (Mean ± SD)

Group → Parameter ↓	Group C (n = 30)	Group D_1 (n = 30)	Group D_2 (n = 30)	P value
Age (y)	34.21 ± 12	35.38 ± 9.56	34.76 ± 11.38	0.837
Weight (kg)	57.07 ± 8.32	59.97 ± 8.99	56.97 ± 10.67	0.194
Sex* (m:f)	17:12	16:13	16:13	0.954
MAC	1.05 ± 0.13	1.01 ± 0.13	1.07 ± 0.1	0.212
Laryngoscopy time(s)	12.07 ± 1.81	12.17 ± 2.24	12.14 ± 2.9	0.970

Table 2

Heart rate (beats per min) at various intervals (Mean ± SD)

Group → Time ↓	Group C	Group D_1	Group D_2	P value
Baseline	79.72 ± 6.98	80.38 ± 9.07	79.96 ± 7.64	0.951
Post-Induction	73.76 ± 12.38	62.17 ± 9.77	61.86 ± 10.22	<0.0001
1 min post-intubation	87.24 ± 7.33	64.31 ± 10.77	63.79 ± 7.97	<0.0001
3 min post-intubation	84.83 ± 9.08	63.66 ± 10.7	62.43 ± 8.32	<0.0001
5 min post-intubation	75.97 ± 11.87	61.45 ± 11.66	59.75 ± 10.46	<0.0001

Table 3

Systolic and Diastolic Blood Pressure (mm Hg) at various intervals (Mean ± SD)

Group → Time ↓	Parameter↓	Group C	Group D_1	Group D_2	P value
Baseline	SBP	113.97 ± 9.06	116.9 ± 9.96	117.36 ± 8.34	0.318
	DBP	73.38 ± 7.74	74.14 ± 6.45	71.32 ± 6.45	0.289
Post-Induction	SBP	100.41 ± 13.73	93.41 ± 10.23	89.82 ± 7.61	0.001
	DBP	66.72 ± 10.1	59.9 ± 7.56	58.39 ± 5.45	0.0003
1 min post-intubation	SBP	120.86 ± 12.74	100.76 ± 12.86	100.43 ± 12.95	<0.0001
	DBP	78.24 ± 8.33	66.69 ± 9.91	63.46 ± 7.66	<0.0001
3 min post-intubation	SBP	113.1 ± 12.09	97.24 ± 11.75	95.79 ± 11.16	<0.0001
	DBP	74.31 ± 7.96	68.45 ± 7.35	66.11 ± 8.43	0.001
5 min post-intubation	SBP	111.14 ± 9.91	95.31 ± 9.66	93.75 ± 10.87	<0.0001
	DBP	72.45 ± 8.77	64.72 ± 6.31	63.21 ± 4.47	<0.0001

Table 4

Mean arterial Pressure (mmHg) at various intervals (Mean ± SD)

Group → Time ↓	Group C	Group D_1	Group D_2	P value
Baseline	84.9 ± 8.69	85.14 ± 4.24	87.14 ± 7.08	0.410
Post-Induction	71.1 ± 10.8	63.21 ± 7.34	62.18 ± 6.3	0.0002
1 min post-intubation	89.34 ± 8.65	70.72 ± 9.98	70.43 ± 8.32	<0.0001
3 min post-intubation	86.34 ± 8.46	71.1 ± 8.5	70.21 ± 5.81	<0.0001
5 min post-intubation	85.31 ± 8.39	69.52 ± 6.95	68.04 ± 6.15	<0.0001

Table 5

Sedation scores and propofol requirement

Group → Parameter ↓	Group C	Group D_1	Group D_2	P value
Sedation scores (Baseline)	1.52±0.51	1.48±0.51	1.55±0.51	0.872
Sedation scores (after pre-medication)	1.52±0.57	2.21±0.68	2.48±0.57	<0.00010
Propofol (mg)	118.41±15.4	100.69±17.31	97.59±14.55	<0.00010

After induction, a fall in SBP, DBP, and MAP was observed in all the groups. In group C, there was an increase in SBP, DBP and MAP at 1 and 3 after intubation. At 5 minutes SBP, DBP and MAP were not statistically different from the baseline in group C. In group D_1 and group D_2, there was a decrease in SBP, DBP and MAP from the baseline at 1, 3, and 5 minutes following intubation. There was statistically significant difference in SBP, DBP, MAP post induction and at 1, 3 and 5 minutes of intubation between group C and group D_1 and group D_2. (Tables 3 and 4)

Baseline sedation scores (Ramsay sedation score) were similar in all the three groups. After pre-medication, sedation score was significantly increased in group D_1 and group D_2 as compared to group C ($p < 0.0001$) as shown in Table 5.

Induction dose of propofol required was found to be 118.41 mg in group C, 100.69 mg group D_1 and 97.59 mg in group D_2 (Table 5). The difference was found to be statistically significant ($p < 0.0001$).

Bradycardia (HR <60 bpm) was seen in 20% of cases in group D_2 and 6.66% of cases in group D_1. None of the patients in group C developed bradycardia. Hypotension (SBP <30%) was observed in 13.3% of cases in group D_2 and 6.66% of cases in group D_1. None of the patients in group C had any episode of hypotension.

Hypotension, bradycardia or respiratory depression were no longer observed 30 minutes after premedication in any of the groups.

Discussion

The sympathetic stimulation leading to tachycardia and hypertension following laryngoscopy and intubation is always of concern to the anaesthesiologist. Sympatholytic effects of dexmedetomidine may be beneficial in attenuating hemodynamic response to laryngosocpy and intubation. The hemodynamic effects of dexmedetomidine have been studied in human volunteers and are seen to be biphasic (12,13). Initial rise in blood pressure with reflex bradycardia may be seen due to effects on peripheral $\alpha_{2\beta}$ receptors. Later post synaptic activation of central α_{2A} and imidazoline type I receptors leads to decrease in sympathetic activity from the locus ceruleus causing sympatholysis and hypotension (14-16). Bradycardia is seen due to decrease in release of noradrenaline caused by presynaptic activation of α_2 receptors (17,18).

We planned a study to explore effectiveness of intranasal dexmedetomidine for attenuation of hemodynamic effects to laryngoscopy and intubation in adults. Intranasal administered dexmedetomidine has a more gradual onset as compared to the intravenous route and thus, early hypertension and reflex bradycardia as seen with rapid intravenous infusion are avoided. Dexmedetomidine is well accepted as premedication as it is tasteless and non-irrritant. In addition to being advantageous in morbid obese and pediatric patients, it can also be administered to adult patients where oral premedication is not feasible. There is no need for two sets of drugs (one for premedication and another for blunting hemodynamic response to laryngoscopy and intubation).

In our study, we observed a fall in heart rate and blood pressure and all hemodynamic parameters remained below baseline even after intubation in patients who were premedicated with intranasal dexmedetomidine.

Similar results were observed in a study by Wang et al. in children undergoing adenotonsillectomy. Intranasal dexmedetomidine 2 µg/kg administered

30 minutes before anesthesia induction was found to effective in blunting hemodynamic response (MAP and HR) to laryngoscopy and intubation (10).

However, results of our study do not completely match with the study by Jayaraman et al. who reported blunting of heart rate but not mean arterial pressure with the use of intranasal dexmedetomidine (1 μg/kg) in morbid obese patients (9).

There can be several reasons for the difference in results. The pharmacodynamic and pharmacokinetic properties in morbid obese may be different, only a single reading of hemodynamic parameters was noted and moreover, the above study was not powered to detect hemodynamic responses to laryngoscopy and intubation.

In our study, we observed a higher sedation score in both the dexmedetomidine groups as compared to the control group, showing the effectiveness of intranasal dexmedetomidine as premedication in adults.

Similar results were seen when intranasal dexmedetomidine 1 μg/kg was given 45 minutes prior to surgery in adult patients undergoing third molar surgery under local anesthesia. Patients were more sedated with intranasal dexmedetomidine as compared to intranasal saline group (19).

We observed a decrease in the requirement of propofol for induction in patients sedated with intranasal dexmedetomidine. The requirement of propofol and alfentanil was found to be significantly less in the intranasal dexmedetomidine group as compared to the saline group in a patient-controlled sedation protocol for upper gastrointestinal endoscopy (20).

Kakkar et al. studied the effectiveness of intravenous infusions of dexmedetomidine (0.5 and 1μg/kg) on hemodynamic response to intubation and compared them with clonidine 1 μg/kg. Intubation response was similar in all the three groups. However, bradycardia was observed in both dexmedetomidine groups and there was a higher incidence of hypotension in the dexmedetomidine 1μg/kg group (5).

We observed a higher incidence of bradycardia (20%) with intranasal dexmedetomidine 2 μg/kg as compared to the other groups. Episodes of bradycardia were found to be easily treatable using atropine. Coughing was observed in some of the patients at the time of nasal instillation of all the study drugs. It could be due to the 2 mL of volume used. We suggest use of a smaller volume for nasal premedication and use of an atomizer.

One limitation of our study was the lack of invasive monitoring to measure the hemodynamic variables. This could have been more reliable than noninvasive monitoring. Another limitation was the lack of anesthetic depth monitoring to evaluate the sedative effects of intranasal dexmedetomidine.

Conclusion

Intranasal dexmedetomidine (1 μg/kg and 2μg/kg) effectively attenuates hemodynamic changes associated with laryngoscopy and intubation in adult patients undergoing elective surgery. However, dexmedetomidine 2μg/ kg is associated with a higher incidence of bradycardia. Intranasal dexmedetomidine also provides effective preoperative sedation and decreases the dose of propofol required for induction of anesthesia. We think this study may encourage other authors in elaborating further the role of intranasal dexmedetomidine for sympatholysis and sedation in adult patient care.

References

1. Malade A and Sarode V. 2007. Attenuation of hemodynamic response to endotracheal intubation : Fentanyl v/s lignocaine. Internet J Anesthesiol. 12: 10954-64.
2. Yuen VM, Hui TW, Irwin MG and Yuen MK. 2008. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in paediatric anesthesia : A double-blinded randomized controlled trial. Anesth Analg. 106: 1715-21.
3. Sebastian B, Talikoti, AT and Krishnamurthy D. 2017. Attenuation of haemodynamic responses to laryngoscopy and endotracheal intubation with intravenous dexmedetomidine : A comparison between two doses. Indian J Anaesth 61: 48-54.
4. Sulaiman S, Karthekeyan RB, Vakamudi M, Sundar AS, Ravullapalli H and Gandham R. 2012. The effects of dexmedetomidine on attenuation of stress response to endo tracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. Ann Card Anaesth 15: 39-43.
5. Kakkar A, Tyagi A, Nabi N, Sethi AK and Verma UC. 2016. Comparison of clonidine and dexmedetomidine for attenuation of laryngoscopy and intubation response - A randomized controlled trial. J Clin Anesth. 33: 283-8.
6. Yuen VM, Hui TW, Irwin MG, Yao TJ, Wong GL and Yuen MK. 2010. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children. Anaesthesia 65: 922-9.
7. Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, Scheinin M and Olkkola KT. 2011. Bioavailability of dexmedetomidine after intranasal administration. Eur J Clin Pharmacol. 67: 825-31.
8. Li A, Yuen VM, Goulay-Dufaÿ S, Sheng Y, Standing JF and Kwok PCL et al. 2018. Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. Br J Anaesth. 120: 960-8.
9. Jayaraman L, Sinha A and Punhani D. 2013. A comparative study to evaluate the effect of intranasal dexmedetomidine versus oral alprazolam as a premedication agent in morbidly obese patients undergoing bariatric surgery. J Anaesthesiol Clin Pharmacol *29*: 179-82.

10. Wang SS, Zhang MZ, Sun Y, Wu C, Xu WY and Bai J et al. 2014. The sedative effects and the attenuation of cardiovascular and arousal responses during anesthesia induction and intubation in pediatric patients : a randomized comparison between two different doses of preoperative intranasal dexmedetomidine. Paediatr Anaesth 24: 275-81.
11. Ramsay MA, Savege TM, Simpson BR and Goodwin R. 1974. Controlled sedation with alphaxalone-alphadolone. Br Med J 2: 656-9.
12. Dyck JB, Maze M, Haack C, Vuorilehto L and Shafer SL. 1993. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology 78: 813-20.
13. Bloor BC, Ward DS, Belleville JP and Maze M. 1992. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology 77: 1134-42.
14. Khan ZP, Ferguson CN and Jones RM. 1999. Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. Anaesthesia 54: 146-65.
15. Correa-Sales C, Rabin BC and Maze M. 1992.A hypnotic response to dexmedetomidine, an alpha-2 agonist, is mediated in the locus coeruleus in rats. Anesthesiology 76: 948-52.
16. Kamisaki Y, Ishikawa T, Takao Y, Omodani H, Kuno N and Itoh T.1990. Binding of [3H] p-aminoclonidine to two sites, alpha 2-adrenoceptors and imidazoline binding sites : distribution of imidazoline binding sites in rat brain. Brain Res. 514: 15-21.
17. Gertler R, Brown HC, Mitchell DH and Silvius EN. 2001. Dexmedetomidine : a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent) 14: 13-21.
18. Aantaa R, Kanto J, Scheinin M, Kallio A and Scheinin H. 1990. Dexmedetomidine, an alpha 2-adrenoceptor agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. Anesthesiology 73: 230-5.
19. Cheung CW, Ng KF, Liu J, Yuen MY, Ho MH and Irwin MG. 2011. Analgesic and sedative effects of intra nasal dexmedetomidine in third molar surgery under local anaesthesia. Br J Anaesthesia 107: 430-7.
20. Cheung CW, Qiu Q, Liu J, Chu KM and Irwin MG. 2015. Intranasal dexmedetomidine in combination with patient-controlled sedation during upper gastrointestinal endoscopy : A randomised trial. Acta Anaesthesiol Scand. 59: 215-23.