International Journal of Research in Medical Sciences
Agarwal S et al. Int J Res Med Sci. 2016 Sep;4(9):4026-4032
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20162928

Research Article

Comparative evaluation of dexmedetomidine with clonidine as premedication for attenuation of hemodynamic responses during laryngoscopy and endotracheal intubation under general anesthesia

Salony Agarwal*, Kumkum Gupta, V. P. Singh, Deepak Sharma, M. N. Pandey

Department of Anaesthesiology and Critical care, Subharti Medical College, Swami Vivekanand University, NH-58. By Pass Road, Meerut, Uttar Pradesh, India

Received: 06 July 2016
Revised: 20 July 2016
Accepted: 04 August 2016

***Correspondence:**
Dr. Salony Agarwal,
E-mail: drsumitsalonyagarwal@gmail.com

ABSTRACT

Background: Direct laryngoscopy and tracheal intubation predictably leads to tachyarrhythmia and hypertension which are usually transient and variable, but these changes may be fatal in high risk patients. These hemodynamic responses can be attenuated by appropriate premedication. Dexmedetomidine and clonidine, alpha- 2 adrenergic agonist, might do so. The present study was aimed to compare these drugs for attenuation of hemodynamic responses.
Methods: Sixty adult consented patients of ASA grade I and II between 18-58 yrs of age of either sex were randomly allocated into two equal groups of 30 patients each by computer generated random number table. They were administered either dexmedetomidine (Group A) or clonidine (Group B) in dose of 1µg.kg-1 intravenously as premedication. Hemodynamic changes during laryngoscopy and intubation were primary end points and any side effects due to drugs were observed as secondary end points.
Results: After propofol induction there was more fall in heart rate in patients of dexmedetomidine group as compared to clonidine group but with statistically non-significant difference (p value>0.05). After laryngoscopy and intubation, hemodynamic variations were more in patients of clonidine group than in dexmedetomidine group with statistically significant difference (p value<0.05). Bradycardia (HR<50/min) was observed in one patient of dexmedetomidine group and two patients in clonidine group, five minutes after intubation. Intraoperative hypotension was observed in one patient of dexmedetomidine group and in two patients of clonidine group.
Conclusions: Dexmedetomidine premedication in dose of 1 µg.kg-1 provided more stable hemodynamics during induction with propofol and following laryngoscopy and intubation as compared to clonidine.

Keywords: Dexmedetomidine, Clonidine, Hemodynamic response

INTRODUCTION

Endotracheal intubation is the most frequently performed procedures in anesthesia practice. It is the trans-laryngeal placement of a tube in the trachea but its clinical benefits are not without undesirable side effects. Direct laryngoscopy and tracheal intubation predictably leads to transient and variable tachyarrhythmia and hypertension. Usually these changes are well tolerated by healthy individuals, but may prove to fatal in patients with untreated severe hypertension, coronary artery disease or intracranial aneurysm. The cardiovascular response is a reflex phenomenon and is mediated by vagus and glossopharyngeal nerve which activate the vasomotor centre to lead a peripheral sympathetic adrenal response.[1] The appropriate premedication, smooth induction and rapid intubation would prevent these associated risks of hemodynamic pressor response. Various pharmacological methods are evaluated either in the premedication or during induction to attenuate these adverse hemodynamic

responses of laryngoscopy and intubation, such as inhalational anesthetics, lidocaine, narcotic analgesics, topical anaesthetic, beta blockers, calcium channel blockers, ACE inhibitors and vasodilators but with variable results. As none of the above methods were proved to be ideal, the search of an ideal agent to attenuate the hemodynamic responses is still continuing.

Dexmedetomidine and clonidine, an α_2 adrenergic agonist, have been used to induce preoperative sedation, intraoperative reduction of anaesthetic and analgesic requirements and hemodynamic stability along with postoperative analgesia. These pharmacological effects made them suitable for premedication for general anesthesia.

The present prospective double blind randomized study was aimed to compare the clinical efficacy of dexmedetomidine (1µg. kg $^{-1}$) with clonidine (1µg. kg $^{-1}$) as intravenous premedication for attenuation of the hemodynamic responses of laryngoscopy and intubation.

METHODS

After approval from Institution Ethical Committee and written informed consent, the present prospective double blind randomized study was performed on 60 adult patients of American Society of Anaesthesiologtst (ASA) physical status I and II aged between 18years to 58 years of either sex, scheduled for elective surgical procedure under general anesthesia with endotracheal intubation.

A detailed history and clinical examination was done before enrolling them for the present study. Patients with severe cardiac or pulmonary disease, uncontrolled hypertension, morbid obesity, psychiatric disease, severe renal or hepatic derangement or patient requiring more than one attempt for intubation, were excluded from the study. All patients were admitted prior to day of surgery and premedicated with Tablet alprazolam 0.5 mg and tablet ranitidine 150 mg the night before surgery. They were kept fasting for 8hrs prior to surgery.

They were randomly divided into two equal groups of 30 patients each according to computer generated random number table. Patients of Group A received intravenous dexmedetomidine in dose of 1 µg.kg^{-1} as premedication and patients of Group B received intravenous clonidine in dose of 1 µg.kg^{-1} as premedication, 10 min before the induction of anesthesia. Both, the anesthesiologist and the patients were blinded about the treatment group and all recordings were done by an resident anesthesiologist, who was unaware of group allocation.

On arrival at operation theatre, routine monitors for heart rate, systemic arterial pressure (NIBP) peripheral oxygen saturation (SpO_2) and electrocardiography (ECG) were attached and baseline vital parameters were recorded. An intravenous line was established and lactated Ringer was started at rate of 6-8 mL/kg. Patients were premedicated with either dexmedetomidine 1 µg. kg^{-1} diluted in 10 ml normal saline or clonidine 1 µg. kg^{-1} diluted in 10 ml normal saline, infused over in 10 minutes with infusion pump, before induction of anesthesia according to group allocation.

Study medication was prepared by an anesthesiologist who was blinded to the randomization schedule and was not further involved for data collection. All patients were given midazolam (0.02 mg/kg), glycopyrrolate 0.2 mg, and tramadol 100 mg intravenously. After preoxygenation for 3 minutes with 100 % oxygen, patient were induced with propofol (2 mg / kg), followed by vecuronium bromide (0.1 mg / kg) to facilitate direct laryngoscopy and intubation.

They were mechanically ventilated and anesthesia was maintained with isoflurane, nitrous oxide 60% in oxygen. The tidal volume and ventilatory frequency were adjusted to maintain end tidal carbon dioxide ($EtCO_2$) between 35-40 mm of Hg.

At the end of the surgery residual neuromuscular blockade was antagonized with appropriate doses of neostigmine (0.05mg / kg) and glycopyrrolate (0.01mg / kg). Extubation was performed when respiration became adequate in tidal volume and the patient was able to obey simple verbal commands. Patients were transferred to post anesthesia care unit for monitoring of sedation, hemodynamic abnormalities, postoperative shivering, respiratory depression, nausea and vomiting or any other drug related side effects and treated according to clinical protocol.

The blood pressure, heart rate, ECG and SpO_2 were recorded at baseline, after study drug infusion, after induction, then immediately after intubation at 1 min interval till 10 min, then at 15 min after intubation. Routine monitoring was continued at 5 min interval till the end of surgery and after extubation.

For present study, any changes in blood pressure and heart rate of more than 20% of baseline values were taken as hypertension/hypotension and tachycardia /bradycardia. The sample size was based in order to detect a significant difference of hemodynamic parameters between the two groups for type 1 error of 0.05 and power of 80%, which indicated that approximately 23 to 25 patients should be included in each group. Assuming a 5% dropout rate, the final sample size was set at 60 patients.

The data obtained in the study are presented in tabulated manner and are expressed as mean±SD and analyzed using Stat graphics Centurion (version 16.2) The parameters of the two groups were compared using student 't' test, chi-square test and ANOVA as applicable. P value <0.05 was considered statistically significant.

RESULTS

The present study compared the clinical efficacy for attenuation of hemodynamic pressor responses by dexmedetomidine or clonidine premedication in dose of 1 µg. kg-1 on 60 adult consented patients of both gender, scheduled for surgery under general anesthesia. Data of all patients were included for statistical analysis. The demographic profiles of the patients were comparable in respect of age, sex, weight and ASA physical status (Table 1).

Table 1: Demographic profile of 60 patients.

Demographic data	Group A	Group B	P value
Age (Year)	37.77±10.92	36.50±9.94	0.640
Weight (Kg)	56.67±9.27	57.80±12.24	0.688
Sex (M:F)	12: 18	14:16	0.57
ASA (I/II)	16/14	17/13	0.82

Data are expressed in mean and SD, p value >0.05 is statistically insignificant.

Table 2: Changes in mean Heart rate.

Heart rate (beats/ minute)	Group A		Group B		
	Mean	SD	Mean	SD	P value
Baseline	86.70	12.237	88.57	12.591	0.563
After induction	70.97	7.850	73.47	9.758	0.218
After intubation heart rate at					
1 min	90.20	11.436	98.50	10.527	0.0049*
3 min	85.80	12.743	93.37	11.047	0.017*
4 min	80.27	12.871	91.33	10.250	0.001**
5 min	78.67	11.851	84.07	9.670	0.058*
10 min	75.30	11.475	80.77	8.152	0.154
15 min	74.67	14.782	78.07	8.694	0.219

Data are expressed in mean and SD, *p <0.05 is statistically significant, **p<0.001 is statistically highly significant.

Hemodynamic profile

Both groups were comparable in respect to baseline hemodynamic profile. No significant difference was observed between the two groups at baseline heart rate, systolic and diastolic blood pressure and mean arterial pressure (p>0.05).

Changes in heart rate

Baseline heart rate of patients were 86.70±12.23 (Group A) and 88.57±12.59 (Group B) beats/min with no significant intergroup difference (p=0.563).

After induction, there was fall in mean heart rate in both the groups but changes were not statistically significant between the groups (p value=0.218). After intubation, heart rate increased in all patients but the increase was more in patients of clonidine group when compared to dexmedetomidine group. There was statistically significant difference in heart rate between the two groups at 1, 2 , 3 and 4 min interval after intubation (p value<0.05). Thereafter the difference of mean heart rate did not show statistically significant inter group difference till 15 minute in subsequent time interval (p value>0.05) (Table 2).

Changes in systolic blood pressure (SBP)

Preoperatively, there was no significant difference in mean SBP between groups. After induction, there was fall in systolic blood pressure in both groups but it was not statistically significant (p value>0.05). After intubation, SBP increased in all patients but the increase was more in patients of clonidine group as compared to dexmedetomidine group. The difference was statistically significant after intubation at interval of 1, 2 and 3 min (p value<0.05). Further difference was not significant as the time advanced (Table 3).

Diastolic blood pressure (DBP)

The baseline mean diastolic blood pressure was comparable between the two groups (p value>0.05). It decreased after induction in both group with no statistically significant intergroup difference (p value>0.05) but it increased after intubation. The patients of clonidine group showed marked increase in DBP in comparison to dexmedetomidine group. There was

statistically significant difference (in diastolic blood pressure) between two groups at 1, 2 and 3 min interval after intubation (p value<0.05). Thereafter, there was no statistically significant changes occurred in diastolic blood pressure in patients of both groups (p value>0.05) (Table 4).

Table 3: Changes in mean systolic blood pressure.

Systolic Blood Pressure (mmHg)	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	130.87	15.930	127.73	15.003	0.436
After induction	125.03	18.438	125.63	15.758	0.893
After intubation SBP at					
1 min	131.20	12.167	137.27	10.084	0.030*
2 min	129.87	12.722	136.53	10.376	0.03*
3 min	124.63	15.399	132.20	13.538	0.04*
4 min	123.90	19.681	127.87	12.789	0.522
5 min	123.73	18.529	125.83	13.004	0.791
10 min	118.30	12.038	122.73	16.235	0.234
15 min	118.60	13.773	121.93	16.000	0.391

Data are expressed in mean and SD,* p <0.05 is statistically significant

Table 4: Changes in mean diastolic blood pressure.

Diastolic blood pressure (mmHg)	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	84.67	7.053	82.50	18.732	0.297
After induction	80.70	8.268	80.90	17.476	0.955
After intubation DBP at					
1 min	84.30	8.543	90.47	10.192	0.013*
2 min	77.97	11.397	86.03	9.978	0.005*
3 min	72.07	12.912	80.80	10.604	0.005*
4 min	73.67	11.394	76.50	8.324	0.251
5 min	74.37	13.371	77.70	9.524	0.630
10 min	71.93	10.235	72.77	12.025	0.337
15 min	70.30	11.151	72.57	11.497	0.634

Data are expressed in mean and SD, * p <0.05 is statistically significant

Table 5: Changes in mean arterial pressure.

Mean Arterial Pressure(mmHg)	Group A		Group B		
	Mean	SD	Mean	SD	P value
Baseline	97.03	9.456	95.43	14.783	0.689
After induction	91.07	10.664	92.75	11.034	0.649
After intubation MAP at					
1 min	95.70	12.015	102.61	14.480	0.04*
2 min	93.33	12.967	100.35	9.956	0.02*
3 min	91.40	13.335	97.77	10.187	0.621
4 min	90.00	14.220	96.62	8.593	0.510
5 min	91.03	12.400	95.38	9.330	0.123
10 min	88.10	11.409	91.42	14.046	0.699
15 min	87.23	11.852	90.92	13.547	0.499

Data are expressed in mean and SD, * p <0.05 is statistically significant

Mean arterial pressure (MAP)

Baseline Mean Arterial Pressure of patients was 97.03±9.45 and 95.43±14.78 mm Hg with no statistically significant intergroup difference (p value>0.05). After induction, there was fall in MAP in all patients with no statistically significant difference (p value>0.05).

It increases in both groups after intubation but the increase was more marked in patients of clonidine group with statistically significant difference at 1 min and 2min (p value<0.05). No significant difference between two groups was observed afterwards. (p value>0.05) (Table 5).

Side effects

No significant changes in peripheral oxygen saturation (SpO2) and cardiac rhythm (ECG) were observed in any patients of both groups. Hypotension occurred in three patients of no clinical significance. Bradycardia occurred in three patients and was treated with bolus of 0.6 mg atropine (Table 6).

Table 6: Side effects.

Adverse effect	Group		P value
	Group A N (%)	Group B N (%)	
Hypotension	1/30 (3.33%)	2/30 (6.67%)	1.000
Hypertension	0/30 (0%)	0/30 (0%)	A
Bradycardia	1/30 (3.33%)	2/30 (6.67%)	1.000
Other side effects	0/30 (0%)	2/30 (6.67%)	0.355

DISCUSSION

The present study compared the clinical efficacy of dexmedetomidine with clonidine as premedication on hemodynamic responses of laryngoscopy and intubation on adult patients, scheduled for elective surgery, under general anaesthesia.

Reid and Brace, first described the hemodynamic responses occurring during laryngoscopy and intubation in form of elevated blood pressure, tachyarrhythmia, cough reflex, increased intracranial and intraocular pressure.[2] If no specific measures are taken to attenuate these hemodynamic responses, the heart rate can increase from 26% to 66% depending on the method of induction and arterial blood pressure can increase from 36% to 45%.[3] These adverse hemodynamic responses can affect the outcome of the patient. Attenuation of such responses is of great importance to decrease the perioperative morbidity and mortality.[4]

Dexmedetomidine and clonidine are α_2 adrenergic receptor agonist with unique pharmacological profile of sedation, sympatholysis, analgesia and cardiovascular stability without respiratory depression. Dex-medetomidine is highly selective α_2 receptor agonist having 8 times more affinity and α_2 selectivity compared to clonidine but has shorter duration of action than clonidine.

Dexmedetomidine caused significant reduction in circulating catecholamine with decrease in blood pressure and a modest reduction in heart rate .It provides dose-dependent sedation with easily arousal after anesthesia. This pharmacological profile renders it suitable as premedication during general anesthesia.

Dexmedetomidine is used in intravenous doses varying from 0.25 to 1 µg. kg^{-1} for attenuation of hemodynamic response of intubation.[5-7] A recent study conducted by Saoyroolu AE et al compared the clinical effects of two different doses of Dexmedetomidine (1 µg.kg^{-1} and 0.5 µg. kg^{-1}) on hemodynamic responses of tracheal intubation and concluded that Dexmedetomidine in dose of 1 µg. kg^{-1} was more effective than dexmedetomidine 0.5µg. kg^{-}.[8] In the present study, the dose of Dexmedetomidine 1 µg. kg^{-1} diluted to 10ml in normal saline was infused over in 10 minutes. The selection of doses of Dexmedetomidine was also in accordance with studies done by Varshali MK et al [9]

Clonidine was initially used as antihypertensive agent, but now it is increasingly used as premedication for its clinical benefit of sympatholysis, sedation, anaesthetic sparing and hemodynamic stabilizing effects during intubation and surgery. Zalunrdo et al has shown that intravenous clonidine was better than oral clonidine in attenuating the pressor response.[10] The effects of clonidine on the hemodynamic parameters are dose related. In the present study 1 µg. $kg^{-1}$of intravenous clonidine was used to attenuate the pressor response of laryngoscopy and intubation.

Scheinin B et al **c**oncluded in this study that dexmedetomidine causes significant reduction in circulating catecholamine with a decrease in blood

pressure and heart rate.[11] In the present study, a decrease in heart rate, systolic blood pressure, diastolic blood and mean blood pressure was observed after induction in both groups but the decrease was more in patients who received dexmedetomidine as premedication.

In the present study, we observed increase in heart rate after laryngoscopy and intubation in all patients but the increase was more in patients who received clonidine as premedication. The increase was much less in dexmedetomidine group which may be due to the decrease in the central sympathetic outflow. Bradycardia was observed in 1 patient of dexmedetomidine group and 2 patients in clonidine group, 6 min after intubation which was manageable with intravenous atropine 0.6 mg. Gomez-vazquez ME et al studied the clinical analgesic efficacy and side effects of dexmedetomidine and found bradycardia to be the most frequent adverse effect of this drug.[12]

After intubation, we also observed an increase in blood pressure in all patients but the increase was more marked in patients who received clonidine as premedication. The difference in the increase in systolic and diastolic blood pressure at 1, 2 and 3 min post intubation interval was statistically significant between the two groups (p value<0.05). This trend was attributed to the decrease in central sympathetic outflow in dexmedetomidine group.

Yildiz M et al and Varshali M K et al studied the effect of dexmedetomidine on hemodynamic response to laryngoscopy and intubation and intraoperative anesthetic requirement.[9,13] They concluded that increase in blood pressure and heart rate were significantly less in dexmedetomidine group.

When dexmedetomidine premedication was compared to clonidine, a significant control of blood pressure and heart rate within a normal range was observed in the present study. Various other studies have also concluded that dexmedetomidine is effective in keeping the patient hemodynamically stable during laryngoscopy and intubation as well as throughout the intraoperative period.[14-16] Their observations were in consistence with present study.

A possible limitation of our study was in assessing the postoperative events and complications. The duration and type of surgery was variable. Moreover our study was restricted till 15 min after intubation and many patients were given intravenous Injection Tramadol, as intraoperative rescue analgesia.

CONCLUSION

We concluded that premedication with dexmedetomidine in dose of 1 μg. kg^{-1} has significantly attenuated the hemodynamic pressor responses to laryngoscopy and intubation when compared to clonidine. Dexmedetomidine provided more stable hemodynamics during induction, laryngoscopy and intubation and is proved to be a better drug for premedication during general anesthesia.

ACKNOWLEDGEMENTS

Authors would like to acknowledge the patients on whom we did our study and the technical staff of operation theatre posted in Subharti Medical College.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Bruder N, Ortega D, Granthil C. Consequences and prevention methods of hemodynamic changes during laryngoscopy and intratracheal intubation. Ann fr Anesth Reanim. 1992;11:57-71.
2. Reid LC, Brace DE. Irritation of the respiratory tract and its reflex effect on heart. Surg Gynae Obstet. 1940;70:157-62.
3. Singh H, Vichitvejpaisal P, Gaines GY, White PF. Comparative effect of lidocaine, esmolol and NTG in modifying the hemodynamic response to laryngoscopy and intubation. Clin Anaesth. 1995;7:1155-8.
4. Chraemmer JA¸ rgensen B, Hertel S, Carlsen PF, Bjerre-Jepsen K. Catecholamine response to laryngoscopy and intubation. The influence of three different drug combinations commonly used for induction of anaesthesia. Anaesthesia. 1992;47(9):750-6.
5. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology. 1992;77:1134-42.
6. Sudheesh K, Harsoor SS. Dexmedetomidine in anaesthetic practice: A wonder drug? Ind J Anaesth 2011;55:323-4.
7. Ebert T, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.
8. Saoyroolu AE, Celik M, Orhon Z, Yüzer S, Sen B. Different doses of dexmedetomidine on controlling hemodynamic responses to tracheal intubation. The Internet Journal of Anesthesiology. 2010;27:2.
9. Varshali MK, Sushma L, Ramesh Naphade. Dexmedetomidine attenuates the sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. Ind J Anesth. 2011;55:352-7.
10. Zalunardo MP, Zollinger A, Spahn DR, Seifert B, Radjaipour M, Gautschi K, et al. Effects of intravenous and oral clonidine on hemodynamic and plasma-catecholamine response due to endotracheal intubation. J Clin Anesth. 1997;9:143-7.

11. Scheinin H, Virtanen R, MacDonald E, Lammintausta R, Scheinin M. Dexmedetomidine, a novel alpha 2-adrenoceptor agonist: a review of its pharmacodynamic effects. Prog Neuro-psychopharmacol Biol Psychiatry. 1989;13(5):635-51.
12. Gomez-Vazquez ME, Hernandez-Salazar E, Hernandez-Jimenez A, Perez-Sanchez A, Zepeda-Lopez VA, Salazar-Paramo M. Clinical analgesic efficacy and side effects of dexmedetomidine in the early postoperative period after arthroscopic knee surgery. J Clin Anesth. 2007;19:576-82.
13. Yildiz M, Tavlan A, Tuncer S, Reisli R, Yosunkaya A, Otelcioglu S. Effect of dexmedetomidine on hemodynamic responses to laryngoscopy and intubation: perioperative hemodynamics and anesthetic requirements. Drugs R D. 2006;7:43-52.
14. Savola JM, Ruskoaho H, Puurunen J, Salonen JS, Karki NT. Evidence for medetomidine as a selective and potent agonist at alpha2-adrenoreceptors. J Autonomic Pharmacol. 1986;5:275-84.
15. Zalunardo M. Preoperative Clonidine attenuates stress response during emergence from anaesthesia. Journal of Clinical Anesthesia. 2000;12:343-9.
16. Reddy VS, Shaik NA, Donthu B, Sannala VK, Jangam V. Intravenous dexmedetomidine versus Clonidine for prolongation of bupivacaine spinal anesthesia and analgesia- A randomized double blind study. J Anaesthesiol clin Pharmacol. 2013;29:342-7.

Cite this article as: Agarwal S, Gupta K, Singh VP, Sharma D, Pandey MN. Comparative evaluation of dexmedetomidine with clonidine as premedication for attenuation of hemodynamic responses during laryngoscopy and endotracheal intubation under general anesthesia. Int J Res Med Sci 2016;4:4026-32.