

A comparative study of effect of two different doses of dexmedetomidine for attenuating the haemodynamic response of laryngoscopy and endotracheal intubation

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Abstract

Objectives: To compare effectiveness of two different loading doses: 0.6 µg/kg versus 1µg/kg of Dexmedetomidine for control of hemodynamic changes during endotracheal intubation.

Materials and Methods: In this prospective interventional study, 60 patients of ASA-I and ASA-II scheduled for elective surgeries under general anesthesia were randomly divided into two groups **Group D_{0.6}** (Inj. Dexmedetomidine dose 0.6µg/kg iv) and **Group D₁** (Inj. Dexmedetomidine dose 1µg/kg iv). Pulse, blood pressure, ECG were monitored continuously and recorded before giving the study drug, at 5 and 10 min infusion of the study drug, at induction, at intubation, then at 1,5,10 minutes after intubation. Data were analysed and p<0.05 was considered significant.

Results: At 5 minutes and 10 minutes of drug infusion, Group D₁ had statistically significant fall in HR as compared to Group D_{0.6} (13.5% & 21.2% versus 3.9% & 7.8%). Maximum fall in mean HR was observed at 10 minutes after intubation in Group D_{0.6} (25.1%) and at 10 minutes of drug infusion in Group D₁ (21.23%). At 5 and 10 min of drug infusion, there was fall (23.6%) in SBP from baseline in group D_{0.6}, while Group D₁ showed transient rise (5.74%) from baseline in SBP, which was highly significant difference statistically (p < 0.0001). The maximum fall in SBP in both groups was observed at 10 minutes following intubation.

Conclusion: dexmedetomidine at 0.6 µg/kg loading dose provides significantly better attenuation of haemodynamic responses of laryngoscopy and endotracheal intubation unaccompanied by transient hypertension and bradycardia, which is observed at 1 µg/kg loading dose.

Keywords: Dexmedetomidine, hemodynamic changes and endotracheal intubation, transient hypertension

1. Introduction

Endotracheal intubation has been practiced after its detailing by Rowbatham and Magill in 1921. The process of intubation is a noxious stimuli leading to a period of extreme haemodynamic stress and is accompanied with intense sympathetic activity marked by tachycardia & hypertension.[1] Perioperative stress which is associated with the anaesthesia stimulates an endocrine response which generally stimulates the sympathetic nervous system[2,3].

In 1940, Hemodynamic response to laryngoscopy and intubation was first shown by Reid and Brace [4]. The circulatory perturbations stem from reflex sympathetic discharge due to epipharyngeal and laryngopharyngeal stimulation, and are marked by tachycardia, hypertension and arrhythmias. The magnitude of the response is greater with increasing force and duration of laryngoscopy.[5] This haemodynamic response is generally transient and unpredictable. Transitory hypertension and tachycardia are of no consequence in healthy individuals but both may be

dangerous to those with hypertension, myocardial insufficiency or cerebrovascular diseases[6] leading to many complications such as pulmonary edema, myocardial insufficiency and cerebrovascular accident.[7,8] The circulatory responses evolved by endotracheal intubation is not adequately or predictably suppressed by intravenous anaesthetic induction agents [9-12]. Various investigators made attempts to reduce the sympathetic response to laryngoscopy and intubation which include,

1. Deepening the plane of anaesthesia with inhalational & intravenous anaesthetic agents [10-13].
2. Decreasing the duration of laryngoscopy to less than 15 seconds.
3. Using of drugs like lidocaine, sedatives, vasoactive drugs like sodium nitroprusside, calcium channel blockers, beta blockers[11-13] and other drugs especially alpha 2 agonists like clonidine & dexmedetomidine.[12-14]

There are many advantages of dexmedetomidine as premedicant in anaesthesia setting like sedation, analgesia, anxiolysis & improved hemodynamic stability.

Different studies have used Dexmedetomidine in the dose of 0.6µg/kg body weight [13,14,24,25] and 1µg/kg body weight [15,16,26,27] as intravenous bolus for reducing the haemodynamic response. There is need to know whether 0.6µg/kg body weight or 1µg/kg body weight is the ideal dose for attenuation of haemodynamic response to laryngoscopy and endotracheal intubation. So, the present study is to show the comparison of the effectiveness of two different doses of intravenous Dexmedetomidine, 0.6µg/kg body weight and 1µg/kg body weight for attenuating haemodynamic response to laryngoscopy and endotracheal intubation

1.1 Aims & Objectives

To compare the effectiveness of 1µg/kg BW and 0.6 µg/kg BW Dexmedetomidine given over 10 minutes for control of haemodynamic changes during laryngoscopy and endotracheal intubation by comparing following parameters :

- Change in Heart rate (HR)
- Change in Systolic blood pressure (SBP)
- Change in Diastolic blood pressure (DBP)

2. Materials and Methods

This prospective randomized double blind clinical study was undertaken at Dhiraj Hospital, attached to S.B.K.S. Medical Institute and Research Centre during the period from November 2013 to July 2015. The study was undertaken after obtaining ethical committee clearance as well as informed consent from all the patients.

2.1 Allocation of Groups

Sixty patients posted for elective surgery under general anesthesia were randomly divided into two groups of 30 patients in each as following

Group D_{0.6}: Received Dexmedetomidine at 0.6µg/kg body weight intravenously

Group D₁: Received Dexmedetomidine at 1µg/kg body weight intravenously, over 10 minutes prior to induction.

2.2 Inclusion Criteria:

- ✓ Age more than 18 years
- ✓ ASA-I and II.
- ✓ No known history of allergy, sensitivity or other form of reaction to the study drugs
- ✓ Patient willing to sign informed consent.
- ✓ Mallampatti class I and II

2.3 Exclusion CRITERIA

- ✗ Patient's refusal.
- ✗ ASA III and IV
- ✗ Known case of Heart blocks, sinus bradycardia and Hypotension, autonomic neuropathy
- ✗ Patients on beta blocker drugs
- ✗ Mallampatti class III and IV
- ✗ Allergy to trial drugs.
- ✗ Nasogastric tube insertion
- ✗ Patient undergoing procedures requiring head and neck manipulation

A routine pre-anaesthetic evaluation of each case was done a day prior to surgery. Weight of the patient was measured for calculation of the drug dosage for the study. Thorough clinical examination including physical examination, systemic examination and airway examination was performed. Patients were kept nil orally 6-8 hours prior to surgery. On arrival in Operation Theater, routine premedication and analgesic was administered to patients of both groups and IV fluid started at 4ml/kg/hr. Baseline parameters were observed and recorded using automatic multi-parameter monitor. Group D_{0.6} patients were given iv Dexmedetomidine at 0.6 µg/kg body weight diluted in 10 ml normal saline using syringe infusion pump over 10 minutes. Group D₁ patients were given iv Dexmedetomidine at 1.0 µg/kg body weight diluted in 10 ml normal saline, using syringe infusion pump over 10 minutes. .

After proper pre-oxygenation and 3 min after completion of infusion, all patients were induced with standardized induction protocol. We excluded the patient taking >15 sec. for intubation. Patients were monitored for incidence of bradycardia (HR < 45), Hypotension (reduction in arterial pressure of 30% or more from the baseline) and Hypertension (rise in BP > 30% of baseline value) and fall in SpO₂.

2.4 Following Parameters were studied:

HR, SBP and DBP were compared in both groups, at following intervals.

1. Before giving the test drug
2. At 5 min with ongoing infusion of study drug
3. At completion of infusion of study drug
4. During induction
5. During intubation
6. 1 min, 5 min, & 10 min after intubation

2.5 Statistical Methods

Statistical analysis was done with non-paired (two tailed, independent) student t-test for continuous data. Results were expressed as mean ± SD. The observation data were gathered from proforma, documented in the master chart and they were expressed in the form of charts and tables

3. Results

Both for age and weight, p-value > 0.05; this indicates that there was no statistically significant difference in patients of Group D_{0.6} and Group D (Table 1)

As shown in Table 2, maximum age of a patient was 59 years in Group D_{0.6} whereas minimum age was 24 years. In Group D₁ maximum age of a patient was 59 years whereas minimum age was 21 years.

Mean HR in group D_{0.6} was 83.66 ± 4.34 per min and in group D₁ it was 82.1 ± 6.69 per min at baseline level, which was comparable (p > 0.05). At 5 minutes and 10 minutes of drug infusion, both Group D_{0.6} and Group D₁ had fall in mean HR, But Group D₁ had statistically significant fall in HR as compared to Group D_{0.6} (p < 0.05). At 5 minutes, fall in HR was 3.9% in Group D_{0.6}, and for Group D₁ it was 13.5%.

At 10 minutes, fall in HR was by 7.8% and 21.2%, in Group D_{0.6} and Group D₁ respectively. During induction, during intubation and at 1 minute after intubation, Fall from baseline HR value was noted and this fall remained to be statistically insignificant between both group.(p>0.05) At 5 and 10 minutes after intubation, fall in HR was 20% and 25% in Group D_{0.6}, whereas 14% and 19% in Group D₁ respectively which was a statistically significant difference. Maximum fall in mean HR was observed at 10 minutes after intubation in Group D_{0.6} and it was observed in Group D₁ at 10 minutes of drug infusion. (Table 3)

Baseline SBP between two groups was comparable (p>0.05). There was fall (23.6%) in SBP from baseline value in group D_{0.6} while drug infusion was going on, while Group D₁ showed transient rise (5.74%) from baseline value in SBP at 5 and 10 minutes of drug infusion which was highly significant difference statistically (p <0.0001) The maximum fall in SBP in both groups was observed at 10 minutes following intubation which was 28.4% and 22.8%, in group D_{0.6} and group D₁ respectively, and this difference was also statistically highly significant.(p<0.05) Neither of the group showed deviation in SBP beyond 30% of the baseline value. (Table 4)

The difference in mean DBP between two groups was statistically insignificant (p>0.05). Statistically significant decrease from baseline (-5.4% and -8.9%) in DBP

was observed in group D_{0.6} at 5 and 10 minutes of drug infusion as compared to increase from baseline (+8.2% and +3.7%) which was observed in Group D₁. (p < 0.05) (Table 5)

Table 1: Demographic Characteristics

	Group D _{0.6}	Group D ₁	P-value
Age (years)	43.73 ± 10.09	39.7 ± 12.76	0.1796
Sex (M/F)	13 / 17	17 / 13	
Weight(kg)	64.2 ± 10.98	68.43 ± 10.59	0.1340
ASA (I/II)	16 / 14	18 / 12	

Both for age and weight, p-value >0.05, which indicates that there was no statistically significant difference in patients of Group D_{0.6} and Group D₁. Male to female ratio and ASA grading was equally distributed in both groups.

Table 2: Age Distribution

Age in years	Group D _{0.6}		Group D ₁	
	No.	%	No.	%
20-30	3	10%	10	33%
31-40	9	30%	5	17%
41-50	8	27%	7	23%
51-60	10	33%	8	27%

The Table 2 shows distribution of age in both the groups. In Group D_{0.6} maximum age of a patient was 59 years whereas minimum age was 24 years. In Group D₁ maximum age of a patient was 59 years whereas minimum age was 21 years.

We have sufficient patients in each age group.

Table 3: Comparison of changes in mean Heart Rate (HR) between Group D_{0.6} & Group D₁

Time	Group D _{0.6}		Group D ₁		P- Value
	Mean ±SD	% Change from baseline	Mean ± SD	%Change from baseline	
Base	83.57 ± 4.29		82.1 ± 6.69		0.3164
5 min with ongoing drug infusion	79.67 ± 1.3	-3.9	68.57 ± 1.33	-13.53	<0.0001
at completion of drug infusion	75.77 ± 1.74	-7.80	60.87 ± 2.29	-21.23	<0.0001
during induction	68.47 ± 4.66	-15.1	69.33 ± 2.55	-12.77	0.3752
during intubation	75.83 ± 3.36	-7.74	77.57 ± 2.91	-4.53	0.0370
1 min after intubation	71.5 ± 2.64	-12.07	72.73 ± 1.98	-9.37	0.0450
5 min after intubation	63.03 ± 2.04	-20.54	67.4 ± 2.08	-14.70	<0.0001
10 min after intubation	58.47 ± 2.75	-25.1	62.17 ± 1.42	-19.93	<0.0001

Table 6 shows comparison of changes in Heart Rate (HR) between two groups and intragroup changes in mean Heart Rate from basal Heart Rate at different time intervals.

Table 4: Comparison of changes in mean systolic blood pressure (SBP) between Group D_{0.6} & Group D₁ (in mmHg)

Time	Group D _{0.6}		Group D ₁		P- Value
	Mean ±SD	% Change from baseline	Mean ± SD	%Change from baseline	
Base	121.43 ± 9.71		120.93 ± 10.73		0.8505145
5 min with ongoing drug infusion	97.8 ± 2.66	-23.63	126.67 ± 9.3	5.74	<0.0001
at completion of drug infusion	97.8 ± 2.66	-23.63	126.67 ± 9.3	5.74	<0.0001
during induction	98.57 ± 4.79	-22.86	106.63 ± 2.5	-14.30	<0.0001
during intubation	105.4 ± 4.99	-16.03	109 ± 6.68	-11.93	0.0213756
1 min after intubation	105.8 ± 3.78	-15.63	105.1 ± 2.96	-15.83	0.4281475
5 min after intubation	97.93 ± 5.2	-23.50	99.57 ± 2.98	-21.36	0.1408568
10 min after intubation	93 ± 3.4	-28.43	98.13 ± 2.18	-22.8	<0.0001

Table 4 shows comparison of changes in mean systolic blood pressure between two groups and intragroup change in mean SBP from basal SBP at different time intervals.

Table 5: Comparison of changes in mean diastolic blood pressure (DBP) between Group D_{0.6} & Group D₁ (in mmHg)

Time	Group D _{0.6}		Group D ₁		P- Value
	Mean \pm SD	% Change from baseline	Mean \pm SD	% Change from baseline	
Base	74.63 \pm 8.92		72.13 \pm 6.29		0.214781
5 min with ongoing drug infusion	69.17 \pm 7.84	-5.46	80.33 \pm 7.24	8.20	<0.0001
at completion of drug infusion	65.73 \pm 7.11	-8.90	75.87 \pm 7.38	3.74	<0.0001
during induction	62.77 \pm 5.21	-11.86	70.03 \pm 5.03	-2.10	<0.0001
during intubation	70.67 \pm 6.75	-3.96	75.13 \pm 4.26	3.00	0.003305
1 min after intubation	70.33 \pm 6.41	-4.30	78.57 \pm 3.94	6.44	<0.0001
5 min after intubation	65.63 \pm 3.63	-9.00	69.4 \pm 2.03	-2.73	<0.0001
10 min after intubation	61.97 \pm 3.56	-12.66	56.57 \pm 3.99	-15.56	<0.0001

Table 5 shows comparison of changes in mean diastolic blood pressure between two groups and intragroup changes in mean DBP from basal DBP at different time intervals.

4. Discussion

Laryngoscopy and endotracheal intubation are perceived as the most detrimental events giving rise to a transient, but marked, sympathoadrenal response. But in patients with cardiovascular compromise like hypertension, coronary artery disease, and cerebrovascular disease and in patients with intracranial aneurysms, even these transient changes in haemodynamics can result in potentially harmful effects[17,18] which necessitates its control[19,20,21] either by pharmacological and non-pharmacological methods, but no single anaesthetic technique is effective in completely abolishing these responses. The drugs used were either partially effective or were with adverse effects.[22]

Dexmedetomidine offers a unique pharmacological profile with sedation, sympatholysis, analgesia, cardiovascular stability and with great advantage to avoid respiratory depression in adult and paediatric patients. It increases the hemodynamic stability by altering the stress induced sympathoadrenal responses to intubation during surgery and during emergence from anesthesia.[14]

Martina Aho *et al*[13], B. Scheinin *et al*[14], R Saraf *et al*[23] and S Gandhi *et al*[24] have studied the stress response attenuating effects of dexmedetomidine at loading dose of 0.6 μ g /kg in different studies, whereas the same parameters have been studied at dose of 1 μ g /kg by other investigators like V Keniya *et al*[16], A Laha *et al*[25], B Kumar *et al*[26], N Gonus *et al*[27] etc, But very few researchers have studied a comparison between these two doses of dexmedetomidine and it is yet remains undetermined which dose of dexmedetomidine provides better attenuation of haemodynamic surges associated with laryngoscopy and intubation. Hence, we have conducted a prospective and comparative study of effect of two different doses (0.6 μ g /kg v/s 1 μ g /kg) of Dexmedetomidine for attenuating the haemodynamic response of laryngoscopy and endotracheal intubation.

In this study 60 patients were randomly assigned to two groups of 30 patients each. Both groups were comparable with respect to demographic and operational factors. No statistically significant differences were found with respect to age, gender, body weight ($P > 0.05$), ASA physical status and the anaesthetic technique did not differ among the study

groups. We had adequate number of patients in each age group range and body weight range (table 2 and 4).

4.1 Heart Rate

The baseline mean HR in Group D_{0.6} was 83.57 \pm 4.29 / minute, whereas it was 82.1 \pm 6.69 /minute in Group D₁, thus, both the groups were comparable with respect of baseline HR value without any significant statistical difference ($p > 0.05$)

There was a statistically significant fall in HR from baseline in Group D₁ at 5 and 10 minutes of drug infusion as compared to Group D_{0.6} where the fall in HR from baseline was not significant. The difference between mean HR in both group at given time interval was also statistically significant ($p < 0.05$). (Table 3)

Similar to our study, A Laha *et al*[26] observed a statistically significant fall in mean HR at 1 and 2 minutes of infusion of dexmedetomidine at 1 /kg over 10 minutes. Transient bradycardia was observed by Kenya *et al*[16] also in their study using infusion of dexmedetomidine at 1 /kg over 10 minutes prior to induction. Significant transient fall in HR at 1st and 5th minute after administration of single dose of 2 /kg was observed by Lawrence *et al*[28]. Nemin Gogus *et al*[27] have shown decrease in HR after the infusion of 1 μ g /kg of Dexmedetomidine.

During induction and intubation, transient fall in mean HR observed at above time interval in Group D₁ had reversed and it remained comparable to Group D_{0.6}. ($p > 0.05$)

The rise in mean HR during intubation was greater with Group D₁ as compared to Group D_{0.6}, but still it remained below baseline for the groups. Similarly, Bijoy Kumar *et al*[26] in his study did not find any rise in HR in Dexmedetomidine group. Celik & Orhon[29] has not found any increase in heart rate with 1 μ g/kg of dexmedetomidine, on the contrary they found 9% fall in HR 1 min after intubation.

At 5 and 10 minutes after intubation, mean HR remained below the baseline value in both groups, but the difference between the mean HR at given time interval was statistically significant ($p < 0.05$), thus, Group D_{0.6} provided more stable haemodynamic condition throughout the stress period.

A biphasic cardiovascular response has been described after the administration of Dexmedetomidine [30] which was observed in our study in Group D₁.

4.2 Blood Pressure

Baseline SBP in Group D_{0.6} was 121.43 ± 9.71 mmHg and it was 120.93 ± 10.73 mmHg in Group D₁. Baseline DBP and MAP was 74.63 ± 8.92 mmHg and 90.23 ± 6.79 mmHg, respectively, in Group D_{0.6}. Likewise, the same was 72.13 ± 6.29 mmHg and 88.4 ± 5.69 mmHg, respectively, in Group D₁. Thus, the baseline blood pressure values between two groups were comparable and there was no statistically significant difference. ($p > 0.05$)

Group D_{0.6} showed fall in mean SBP by 23.6% at 5 and 10 minutes of drug infusion, whereas Group D₁ showed rise in SBP by 5.74 % at above mentioned time interval, which was statistically highly significant ($p < 0.05$), but was transient in nature, as it was followed by fall in mean SBP by 14.3% during induction. (Table 4)

Similar to our study finding, Laha *et al* [26] also found increase in SBP and DBP after 1 and 2 minutes of administration of dexmedetomidine at 1 /kg loading dose, out of which the increase in pressures were statistically significant at 1 minute. Similar increase in BP was further observed and confirmed by Bloor *et al* [30] also. A study by Keniya *et al* [16] also showed that pretreatment with dexmedetomidine 1 /kg attenuated, but not totally obtunded, the cardiovascular response to tracheal intubation.

Our result is also supported by many earlier studies where they have transient increase in HR and MAP initially within 3 to 5 min of dexmedetomidine infusion, which is followed by a decrease [31-34] and is probably due to the vasoconstriction effect of dexmedetomidine appearing earlier than the central sympathetic action.

During intubation and 1 min after intubation, rise in DBP from baseline by 3% and 6.44% was observed in Group D₁, whereas DBP remained below baseline by 3.96% and 4.30% for respective time interval in Group D_{0.6}, thus, the difference was statistically quite significant at 1 minute after intubation. Nermin Gogus *et al* [27] has found 6% rise in DBP after intubation with Dexmedetomidine and Kunisawa *et al* noticed only 3% rise in dexmedetomidine treated patients which was similar to our results.

In both groups SBP & DBP started falling immediately after intubation but rate of fall in BP was more gradual in group D₁. Maximum fall in SBP, DBP and MAP in both the group was observed at 10 minutes following intubation, but still the difference between both group remained statistically significant ($p < 0.05$)

In our study, no patient had bradycardia (HR < 45), hypertension (BP level > 30% over baseline levels), hypotension (BP level < 30% from baseline levels) and any fall in SpO₂ level. Similar to our results Bijoy Kumar Panda [26] and Shirsendu Mondal *et al* [35] have also not found any instability of vitals either with clonidine or

dexmedetomidine. Singh *et al* [36] study also did not show any side effects like bradycardia and sinus pause, which would have warranted the use of atropine. Scheinin *et al* reported that use of α_2 agonist leads to bradycardia. [37] Some study reported that when Dexmedetomidine in 1-2 $\mu\text{g/kg}$ given in two minutes causes irregular ventilation and apnoea episodes. [30]

Coming to a conclusion based on statistical analysis and thereby obtained results, it can be stated that dexmedetomidine at 0.6 $\mu\text{g/kg}$ loading dose provides significantly better attenuation of haemodynamic responses of laryngoscopy and endotracheal intubation unaccompanied by transient hypertension and bradycardia, which is observed at 1 $\mu\text{g/kg}$ loading dose.

Acknowledgments

I am using this opportunity to express my gratitude to everyone who supported me throughout the course of this study. I would like to express the deepest gratitude to all my esteemed teachers, for their constant help support and invaluable guidance. I gratefully acknowledge the help rendered by my seniors, my colleagues and my juniors. I express my thanks to the chancellor; the dean; the medical superintendent, the research director and the registrar of S.B.K.S.M.I.R.C., Sumandeep Vidyapeeth University for allowing me to carry out this work in this institution. I am also thankful to all medical, paramedical and nursing personal for their direct or indirect contribution in making this study possible. I express my thanks to the patients for their participation and co-operation for the study, which made the study possible. Finally, I would like to pay my profound regards to almighty.

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