Randomized, double-blind trial of effects of intravenous Diltiazem with Dexmedetomidine on Hemodynamic responses to laryngoscopy and tracheal intubation

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Abstract

Context: Endotracheal intubation has been suggested to be one of the most invasive stimuli in anesthesia, particularly during induction and after tracheal intubation. The present study aims to evaluate the efficacy of dexmedetomidine as compared to diltiazem on hemodynamic response to laryngoscopy and intubation. **Aims:** To assess and compare the hemodynamic response of dexmedetomidine as compared to diltiazem in patients undergoing laryngoscopy and intubation and rate and type of side effects of the drugs if any. **Settings and Design:** This study design was a prospective, randomized, and double-blind trial. **Subjects and Methods:** The patients were randomly allocated into three groups: Group I (control), Group II (dexmedetomidine), and Group III (diltiazem) of 45 patients each. Group I ($n = 45$): 0.9% NaCl 10 ml was given to the patients over 10 min before intubation in Group I (control). Group II ($n = 45$): injection dexmedetomidine (0.5 µg/kg) in 10 ml normal saline was given to the patients over 10 min before intubation. Group III ($n = 45$): injection diltiazem (0.3 mg/kg) in 10 ml normal saline was given to the patients over 10 min before intubation. **Statistical Analysis Used:** The data so collected were subjected to statistical analysis using Statistical Package for the Social Sciences version 15.0. **Results:** Mean percentage increase in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) following intubation was 17.90%, 19.96%, and 19.04%, respectively, in control group, 9.04%, 6.32%, and 7.53%, respectively, in dexmedetomidine group, and 12.30%, 10.32%, and 11.14%, respectively, in diltiazem groups. Statistically, there was a significant difference in postintubation SBP, DBP, and MAP of the three groups ($P < 0.001$). Dexmedetomidine at a dose of 0.5 µg/kg showed to have a better attenuation of pressor response as compared to diltiazem at a dose of 0.3 µg/kg. **Conclusions:** Both dexmedetomidine and diltiazem were safe and effective in attenuating the hemodynamic response following laryngoscopy and endotracheal intubation; however, between two trial drugs, dexmedetomidine had a better response.
Keywords: Dexmedetomidine, diltiazem, intubation, laryngoscopy, pressure response

Introduction

Endotracheal intubation has been suggested to be one of the most invasive stimuli in anesthesia,[1,2] particularly during induction and after tracheal intubation. The pressor response which is a part of huge spectrum of stress response during laryngoscopy and intubation following general anesthesia is due to sympathoadrenal activity as evidenced by increased heart rate (HR), blood pressure, and serum catecholamine concentrations, described in as early as 1940 by Reid and Brace.[3] Laryngoscopic manipulation and endotracheal intubation are noxious stimuli capable of producing tachycardia, arrhythmias, and hypertension (HTN).[4] Evidence from laboratory data demonstrates that epipharyngeal and laryngopharyngeal stimulation augments cervical sympathetic activity in the heart. This explains the increase in plasma levels of norepinephrine and to lesser extent epinephrine which occurring during airway instrumentation.[5]

This stress response is usually well tolerated by normotensive patients, but even short-lasting stimulation has been associated with increased morbidity and mortality and in patient with recent myocardial infarction, HTN, preeclampsia, thyrotoxicosis, and cerebrovascular pathology such as tumors, aneurysms, or increased intracranial pressure.[3,6-8]

Vasodilators and lidocaine provide an incomplete solution controlling HTN but have no effect on HR. Thus, they have limited use in normotensive patients unless a β-blocker is coadministered. However, β-blockers as well as have a number of known side effects which include bronchospasm, bradycardia, hypotension, heart failure, and cardiac dysrhythmias.[6]

Opioids are widely used to control the neurovegetative response to intubation.[9-13] They have the advantage of having a perioperative role in anesthesia. Diltiazem, a calcium channel blocker (CCB), is traditionally used as antihypertensive drugs, i.e., as medications to decrease blood pressure in patients with HTN. CCBs are particularly effective against large vessel stiffness, one of the common causes of elevated systolic blood pressure (SBP) in elderly patients.[14] It is a benzothiazepine class of compound and is an intermediate class between phenylalkylamine and dihydropyridines in their selectivity for vascular calcium channels.

Another class of anesthetic agents α-agonists has also been used to block the hemodynamic effects and also provides sedative and sympatholytic effects. Clonidine is the prototype drug in this class. Dexmedetomidine is a highly selective α_{-2} receptor agonist. It is 8 times more specific and selective for α_2 adrenoceptors than clonidine and shorter duration of action than clonidine. Dexmedetomidine has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many of cardiovascular responses in the perioperative period. As preanesthetic medication, dexmedetomidine decreases sympathetic, adrenal, and cardiovascular response to laryngoscopy and tracheal intubation.

The present study aims to evaluate the efficacy of dexmedetomidine as compared to diltiazem on hemodynamic response to laryngoscopy and intubation.

Subjects and Methods

The study was carried out in a tertiary care teaching hospital. One hundred and thirty-five adults in the age group of 18–60 years scheduled for surgery under general anesthesia were studied after obtaining the clearance from the Institutional Ethical Committee. Written and informed consent was obtained from eligible patients. The patients were visited a day before surgery for preanesthtic review, and standard institutional preoperative advice was given. Inclusion criteria are adult patients aged 18–60 years, American Society of Anesthesiologists physical classes I and II, and patients undergoing operative procedures requiring laryngoscopy and intubation, whereas exclusion criteria are patients with comorbidities (chronic obstructive pulmonary disease, ischemic heart disease, HTN, diabetes mellitus, renal/hepatic dysfunction, etc.), patients with anticipated difficult intubation: Mallampati Grade III and IV, patients with a known contraindication to any of the study drugs, patients not willing to participate in the study, and patients in whom intubation cannot be done within 2 min of administration of study drugs.

On arrival of patients in the operation theater, intravenous (IV) line was initiated with 18G cannula. Preoperative recording of HR, noninvasive blood pressure (systolic and diastolic and mean arterial pressure [MAP]), and arterial oxygen saturation (SpO_2) was done.

The patients were randomly allocated in three groups: Group I (control), Group II (dexmedetomidine), and Group III (diltiazem) of 45 patients each.

- Group I ($n = 45$): 0.9% NaCl 10 ml was given to the patients over 10 min before intubation in Group I (control)

- Group II ($n = 45$): injection dexmedetomidine (0.5 µg/kg) in 10 ml normal saline was given to the patients over 10 min before intubation

- Group III ($n = 45$): injection diltiazem (0.3 mg/kg) in 10 ml normal saline was given to the patients over 10 min before intubation.

All the patients were premedicated with injection glycopyrrolate (5 µg/kg), ondansetron (0.1 mg/kg), and pentazocine (0.5 mg/kg). Simultaneously, they were preoxygenated with 100% O_2 for 3 min. Before induction, patients were given the drug according to the group allotted to them. After the administration of the respective drug, the patients were induced with injection propofol (1.5 mg/kg). Patients were intubated following the administration of paralyzing dose of injection succinylcholine (1.5 mg/kg) intravenously. Anesthesia was maintained with 50% oxygen in nitrous oxide delivered through Bain's circuit using IPPV and propofol infusion (50 µg/kg/min). Muscle relaxation was achieved with injection vecuronium (0.1 mg/kg) followed by incremental doses of injection vecuronium (0.02 mg/kg).

At the conclusion of surgery, residual muscle paralysis was reversed with injection neostigmine (50 µg/kg) and injection glycopyrrolate (10 µg/kg) intravenously. The patient was extubated following return of regular, rhythmic respiration when reasonably awake.

The following hemodynamic parameters were evaluated:

- SBP
- Diastolic blood pressure (DBP)
- MAP
- HR
- SpO$_2$.

Any clinical side effect throughout the perioperative period (bradycardia, hypotension, sedation, delayed recovery, etc.).

All the above parameters were recorded preoperatively as well as during the intraoperative period. The points of time at which recordings for above parameters were made are as follows:
- T0 - immediately before administration of drug (Baseline)
- T1 - after administration of sample drug

- T2 - after induction of anesthesia
- T3 - just before intubation
- T4 - just after intubation
- T5-1 min after intubation
- T6-2 min after intubation
- T7-5 min after intubation but before surgical incision.

Bradycardia (HR <50 b.p. min.) was planned to be treated with injection atropine 0.6 mg intravenously and hypotension (MAP <20% of baseline or SBP <90 mm Hg) was planned to be treated with 200 ml crystalloid bolus and injection phenylephrine in 100 mcg increments up to maximum of 500 mcg, if required.

Results

The present study was carried out with an aim to assess and compare the hemodynamic response of dexmedetomidine as compared to diltiazem in patients undergoing laryngoscopy and intubation.

A total of 45 (33.3%) patients were randomly allocated to Group I (control group) who were administered 0.9% NaCl 10 ml over 10 min before intubation. Another 45 (33.3%) patients were allocated to Group II, who were administered injection dexmedetomidine (0.5 □g/kg) in 10 ml normal saline over 10 min before intubation. The remaining 45 (33.3%) patients were allocated to Group III, who were administered injection diltiazem (0.3 mg/kg) in 10 ml normal saline over 10 min before intubation.

At baseline, the three groups were matched statistically for age, gender, and grade of surgery and did not show a significant intergroup difference [Table 1].

At baseline, mean SBP ranged from 117.56 ± 9.14 (Group II) to 120.27 ± 9.90 mmHg (Group I), which is statistically nonsignificant (P = 0.343), i.e., the groups were matched at baseline.

At T1, the mean SBP in different groups ranged from 117.67 ± 8.52 mmHg (Group II) to 121.47 ± 10.09 mmHg (Group I), thus again showing statistically no significant intergroup difference.
However, from T2 onward, a significant difference among groups was observed. At all the subsequent intervals, mean value of Group I was maximum whereas Group II had minimum mean value. The trend of change indicated the assumption of maximum mean value by T3 in all the three groups which was subsequently followed by a continuous decline. At T7, mean values in Groups I, II, and III were 123.04 ± 7.80, 114.71 ± 7.63, and 118.49 ± 10.16 mmHg, respectively. Statistically, the intergroup difference was significant (P < 0.001) [Table 2].

Table 1: Demographics and baseline characteristics

Characteristic	Group I (*n*=45)	Group II (*n*=45)	Group III (*n*=45)	Statistical significance
Mean age±SD	36.04±9.59	36.60±8.10	34.29±8.11	F=0.880; P=0.417 (NS)
Male:female	24:21	20:25	29:16	$\chi2$=3.639; P=0.162 (NS)
ASA I/II	27:18	18:27	21:24	$\chi2$=3.735; P=0.154 (NS)

NS=Not significant, SD=Standard deviation, ASA=American Society of Anesthesiologists

On comparing the between-group difference, a statistically significant difference was observed between Groups I and II and between Groups I and III at all the time intervals starting from T2 to T7. At all these time intervals, mean value of Group I was significantly higher as compared to that of Groups II and III. Between Groups II and III, Group II had lower mean value as compared to Group III at all the time intervals; however, the difference between two groups was statistically significant starting from T4 to T7. The difference between two groups was maximum at T5 and minimum at T1 [Table 2a].

Table 2: Intergroup comparison of systolic blood pressure at different time intervals

Time interval	Mean±SD			Statistical significance	
	Group I (*n*=45)	Group II (*n*=45)	Group III (*n*=45)	F	P
T0	120.27±9.90	117.56±9.14	118.11±8.65	1.079	0.343
T1	121.47±10.09	117.67±8.52	117.82±8.57	2.520	0.084
T2	122.51±10.34	116.49±8.72	117.00±8.39	5.940	0.003
T3	123.53±10.76	115.87±7.88	116.11±8.17	10.481	<0.001
T4	141.80±9.62	128.18±7.54	132.64±6.76	33.377	<0.001
T5	135.00±8.96	122.60±7.74	130.36±9.33	23.324	<0.001
T6	129.00±8.45	118.38±7.80	122.69±10.87	15.384	<0.001
T7	123.04±7.80	114.71±7.63	118.49±10.16	10.575	<0.001

SD=Standard deviation

Table 2a: Between-group comparison of systolic blood pressure at different time intervals

Time interval	Group I versus Group II		Group I versus Group III		Group II versus Group III	
	t	P	*t*	P	*t*	P
T0	1.349	0.181	1.100	0.275	−0.296	0.768
T1	1.931	0.057	1.847	0.068	−0.086	0.931
T2	2.986	0.004	2.776	0.007	−0.283	0.778
T3	3.858	<0.001	3.685	<0.001	−0.144	0.885
T4	7.478	<0.001	5.224	<0.001	−2.959	0.004
T5	7.025	<0.001	2.409	0.018	−4.293	<0.001
T6	6.195	<0.001	3.074	0.003	−2.162	0.033
T7	5.124	<0.001	2.386	0.019	−1.994	0.049

On comparing the change from baseline, in Group I, a significant change in mean SBP was observed at all the time intervals. This change ranged from 1% (T1) to 17.90 (T4). Thus, the trend showed an inclining trend till T4 followed by a declining trend.

In Group II, a significant change from baseline was observed at T3, T4, T5, and T7 intervals. Of these, at T3 and T7, mean values were lower as compared to baseline at T3 and T7 and significantly higher as compared to baseline at T4 and T5. Maximum change from baseline was at T4 (9.40%) while minimum change was at T1 (0.09%).

In Group III, a significant change from baseline was observed starting from T2 to T6. At T2 and T3, mean values were lower as compared to baseline, whereas at T4, T5, and T6, mean values were higher as compared to baseline. The mean change was maximum at T4 (12.30%) and minimum at T1 (−0.24%) [Table 2b].

At baseline, mean DBP in Groups I, II, and III was 74.71 ± 6.31, 75.29 ± 8.99, and 77.31 ± 6.67 mmHg, respectively, thus showing no significant intergroup difference (P = 0.222). Statistically, no significant intergroup difference was observed among the groups till T2. However, at subsequent time intervals, a significant intergroup difference was observed among the groups ($P < 0.001$). From T3 onwards, Group I had the maximum values whereas Groups II and III had lower values as compared to Group I. In all the groups, peak DBP value was observed at T4. In Group I, minimum mean value was observed at T2, whereas in Groups II and III, minimum mean value was observed at T7 [Table 3].

Table 2b: Within-group evaluation of change in systolic blood pressure (as compared to baseline) at different time intervals

Time interval	Group I			Group II			Group III		
	Percentage change	t	P	Percentage change	t	P	Percentage change	t	P
T1	1.00	−4.23	<0.001	0.09	−0.24	0.813	−0.24	1.10	0.278
T2	1.87	−4.07	<0.001	−0.91	1.65	0.107	−0.94	2.33	0.024
T3	2.72	−4.18	<0.001	−1.44	2.77	0.008	−1.69	3.42	0.001
T4	17.90	−28.12	<0.001	9.04	−22.22	<0.001	12.30	−22.85	<0.001
T5	12.25	−20.28	<0.001	4.29	−10.44	<0.001	10.37	−15.25	<0.001
T6	7.26	−13.28	<0.001	0.70	−1.52	0.137	3.88	−5.34	<0.001
T7	2.31	−4.74	<0.001	−2.42	5.39	<0.001	0.32	−0.58	0.565

Table 3: Intergroup comparison of diastolic blood pressure at different time intervals

Time interval	Mean±SD			Statistical significance	
	Group I (n=45)	Group II (n=45)	Group III (n=45)	F	P
T0	74.71±6.31	75.29±8.99	77.31±6.67	1.523	0.222
T1	74.87±7.52	73.49±9.21	74.87±7.06	0.447	0.641
T2	73.84±7.20	72.49±9.22	71.67±7.83	0.824	0.441
T3	73.76±6.48	70.91±8.74	67.67±5.70	8.301	<0.001
T4	89.62±10.76	80.04±8.62	85.29±4.94	14.475	<0.001
T5	86.89±11.32	74.82±8.94	80.18±7.54	18.632	<0.001
T6	83.04±10.83	71.67±8.85	76.36±6.47	18.592	<0.001
T7	79.22±10.11	70.76±9.42	71.51±6.15	12.950	<0.001

SD=Standard deviation

Table 3a: Between-group comparison of diastolic blood pressure at different time intervals

Time interval	Group I versus Group II		Group I versus Group III		Group II versus Group III	
	t	P	t	P	t	P
T0	−0.353	0.725	−1.899	0.061	−1.212	0.229
T1	0.777	0.439	0.000	1.000	−0.796	0.428
T2	0.777	0.439	1.373	0.173	0.456	0.649
T3	1.753	0.083	4.732	<0.001	2.086	0.040
T4	4.660	<0.001	2.454	0.016	−3.542	0.001
T5	5.612	<0.001	3.311	0.001	−3.072	0.003
T6	5.458	<0.001	3.557	0.001	−2.870	0.005
T7	4.110	<0.001	4.370	<0.001	−0.450	0.653

No significant difference was observed between Groups I and II till T3; however, thereafter mean value in Group I was significantly higher as compared to Group II till T7. Between Groups I and II too, no significant difference was observed till T2; however, from T2 to T7, mean value in Group I was significantly higher as compared to Group II. On comparing the difference between Groups II and III, the difference was not statistically significant till T2. A significant difference was observed between two groups at T3, T4, T5, and T6 intervals. At T3, mean DBP was significantly higher in Group II as compared to Group III; however, at subsequent intervals, mean value was lower in Group II as compared to Group I, and the difference between two groups was significant too between T4 and T6 intervals [Table 3a].

In Group I, mean DBP showed an incremental trend throughout the study period. Increase in mean DBP as compared to baseline was significantly higher starting from T4 onwards. The mean change was maximum at T4 and showed a minimum value at T1.

In Group II, mean DBP was significantly lower as compared to baseline at all the time periods except at T4 where mean values were higher as compared to baseline. The difference from baseline was significant too at all the time intervals except at T5.

In Group III, mean values were significantly higher as compared to baseline at T4 and T5. At all the other intervals, mean values were lower as compared to baseline, and the difference was also statistically significant except at T6 when the mean value was lower as compared to baseline, but difference was not statistically significant ($P = 0.428$) [Table 3b].

Table 3b: Within-group evaluation of change in diastolic blood pressure (as compared to baseline) at different time intervals

Time interval	Group I			Group II			Group III		
	Percentage change	t	P	Percentage change	t	P	Percentage change	t	P
T1	0.21	−0.46	0.646	−2.39	9.12	<0.001	−3.16	6.58	<0.001
T2	1.16	1.800	0.079	−3.72	8.02	<0.001	−7.30	10.61	<0.001
T3	1.28	1.830	0.074	−5.81	12.02	<0.001	−12.47	14.80	<0.001
T4	19.96	−9.44	<0.001	6.32	−11.09	<0.001	10.32	−7.19	<0.001
T5	16.30	−7.30	<0.001	−0.62	0.93	0.358	3.71	−2.15	0.037
T6	11.15	−5.22	<0.001	−4.81	6.96	<0.001	−1.24	0.80	0.428
T7	6.04	−3.12	0.003	−6.02	4.43	<0.001	−7.50	4.59	<0.001

Table 4: Intergroup comparison of mean arterial pressure at different time intervals

Time interval	Mean±SD			Statistical significance	
	Group I (n=45)	Group II (n=45)	Group III (n=45)	F	P
T0	89.90±5.90	89.07±7.86	90.53±5.94	0.554	0.576
T1	90.40±6.48	87.98±7.58	88.80±5.90	1.524	0.222
T2	89.61±6.61	87.02±7.46	86.51±6.43	2.644	0.075
T3	90.00±5.84	85.60±7.35	83.56±5.38	4.936	<0.001
T4	107.01±7.59	95.78±7.03	100.62±4.27	34.253	<0.001
T5	102.93±7.71	90.40±7.40	96.64±6.91	32.708	<0.001
T6	98.36±7.54	86.89±7.36	91.44±6.46	29.514	<0.001
T7	93.83±7.11	84.96±6.96	86.71±5.92	22.234	<0.001

SD=Standard deviation

Table 4a: Between comparison of mean arterial pressure at different time intervals

Time interval	Group I versus Group II		Group I versus Group III		Group II versus Group III	
	t	P	t	P	t	P
T0	0.566	0.573	−0.511	0.611	−0.999	0.321
T1	1.629	0.107	1.224	0.224	−0.574	0.568
T2	1.740	0.085	2.252	0.027	0.348	0.729
T3	3.144	0.002	5.441	<0.001	1.505	0.136
T4	7.287	<0.001	4.927	<0.001	−3.951	<0.001
T5	7.863	<0.001	4.070	<0.001	−4.140	<0.001
T6	7.307	<0.001	4.675	<0.001	−3.122	0.002
T7	5.982	<0.001	5.162	<0.001	−1.288	0.201

At baseline, mean MAP in Groups I, II, and III was 89.90 ± 5.90, 89.07 ± 7.86, and 90.53 ± 5.94 mmHg, respectively. Statistically, the intergroup difference was not significant ($P = 0.576$). The difference among groups remained statistically not significant till T2. However, a significant difference among groups was observed from T3 to T7. At all these time intervals, Group I had the maximum mean value whereas Groups II and III had significantly lower mean value as compared to Group I ($P < 0.001$) [Table 4].

Between-group comparison of Groups I and II revealed a statistically significant intergroup difference starting from T3 to T7. At all these time intervals, Group I had significantly higher mean value as compared to Group II ($P < 0.001$).

On comparing Groups I and III, a statistically significant difference was observed starting from T2 to T7, and at all these time intervals, mean value in Group I was higher as compared to Group II.

Between-group comparison of Groups II and III showed a statistically significant difference starting from T4 to T5. At all these time intervals, mean value in Group II was significantly lower as compared to Group I [Table 4a].

In Group I, statistically no significant change was observed from baseline to T3. However, from T4 to T7, mean values were significantly higher as compared to baseline. Maximum mean change was observed at T4 (19.04%) and minimum at T3 (0.11%).

In Group II, at all time intervals, the change from baseline was statistically significant. However, it showed an increase only at T4 and T5, at all the other time intervals, there was a mean decrease from baseline. Maximum change was observed as an increase at T4 (7.53%) whereas minimum change was observed as a decrease at T1 (1.22%).

In Group III, the change from baseline was significant statistically at all the time intervals except T6. There was a mean decrease from baseline at all time intervals except at T4, T5, and T6. Maximum change from baseline was observed to be an increase of 11.14% at T4 whereas minimum change was also observed as an increase of 1.01% at T6 [Table 4b].

At baseline, mean HR was 76.91 ± 7.91, 78.18 ± 7.90, and 78.44 ± 7.76 bpm, respectively, in different groups, thus showing statistically no significant difference among groups ($P = 0.614$). A significant difference among groups was observed at T1 itself when mean value was minimum in Group I (73.78 ± 8.42 bpm) and maximum in Group II (78.78 ± 7.69 bpm). Statistically significant differences among groups were observed from T4 to T7. At all these time intervals, mean HR in Group I was maximum ($P < 0.001$) [Table 5].

On between group comparison, mean HR was significantly lower in Group I as compared to Group II at T1 and T3 and was significantly higher as compared to Group II from T4 to T7.

Between Groups I and III, a statistically significant difference was observed from T4 to T7. At all these time intervals, mean value was significantly higher in Group I as compared to Group III.

Table 4b: Within-group evaluation of change in mean arterial pressure (as compared to baseline) at different time intervals

Time interval	Group I			Group II			Group III		
	Percentage change	t	P	Percentage change	t	P	Percentage change	t	P
T1	0.56	−1.99	0.053	−1.22	4.81	<0.001	−1.91	5.77	<0.001
T2	−0.32	0.83	0.412	−2.30	4.68	<0.001	−4.44	9.93	<0.001
T3	0.11	0.26	0.796	−3.89	9.93	<0.001	−7.71	14.46	<0.001
T4	19.04	−15.58	<0.001	7.53	−19.23	<0.001	11.14	−13.94	<0.001
T5	14.49	−11.38	<0.001	1.50	−3.48	0.001	6.75	−5.91	<0.001
T6	9.42	−7.67	<0.001	−2.45	5.38	<0.001	1.01	−1.02	0.312
T7	4.38	−3.91	<0.001	−4.62	4.75	<0.001	−4.22	4.17	<0.001

Table 5: Intergroup comparison of heart rate at different time intervals

Time interval	Mean±SD			Statistical significance	
	Group I (n=45)	Group II (n=45)	Group III (n=45)	F	P
T0	76.91±7.91	78.18±7.90	78.44±7.76	0.489	0.614
T1	73.78±8.42	78.78±7.69	76.24±7.92	4.379	0.014
T2	73.58±8.29	75.80±7.61	73.22±7.85	1.399	0.250
T3	70.93±8.13	77.80±9.48	70.24±7.74	10.921	<0.001
T4	101.27±7.64	83.80±7.55	92.69±8.94	52.725	<0.001
T5	96.71±6.70	76.40±8.97	87.93±6.67	82.505	<0.001
T6	93.16±6.52	75.20±7.73	83.02±5.64	81.621	<0.001
T7	87.69±7.72	72.98±6.97	78.51±6.14	51.132	<0.001

SD=Standard deviation

Table 5a: Between-group comparison of heart rate at different time intervals

Time interval	Group I versus Group II		Group I versus Group III		Group II versus Group III	
	t	P	t	P	t	P
T0	−0.760	0.449	−0.928	0.356	−0.162	0.872
T1	−2.942	0.004	−1.432	0.156	1.539	0.127
T2	−1.324	0.189	0.209	0.835	1.581	0.117
T3	−3.690	<0.001	0.412	0.681	4.143	<0.001
T4	10.907	<0.001	4.892	<0.001	−5.097	<0.001
T5	12.171	<0.001	6.229	<0.001	−6.923	<0.001
T6	11.912	<0.001	7.887	<0.001	−5.484	<0.001
T7	9.491	<0.001	6.245	<0.001	−3.997	<0.001

Between Groups II and III, a significant difference was observed from T3 to T7. At T3, mean value in Group II was higher as compared to Group III; however from T4 to T7, mean value was significantly higher in Group III as compared to Group II [Table 5a].

In Group I, a significant decrease in HR as compared to baseline was observed from T1 to T3; however, at subsequent intervals, a significant increase in HR as compared to baseline was observed. Maximum increase was at T4 (31.67%) whereas minimum increase was at T7 (14.07%). Maximum decrease was at T3 (−7.77%) and minimum decrease was at T1 (−4.07%).

Table 5b: Within-group evaluation of change in heart rate (as compared to baseline) at different time intervals

Time interval	Group I			Group II			Group III		
	Percentage change	t	P	Percentage change	t	P	Percentage change	t	P
T1	−4.07	13.34	<0.001	0.77	−0.60	0.553	−2.80	23.60	<0.001
T2	−4.33	11.65	<0.001	−3.04	2.92	0.006	−6.66	11.89	<0.001
T3	−7.77	14.76	<0.001	−0.48	0.24	0.808	−10.45	13.31	<0.001
T4	31.67	−18.75	<0.001	7.19	−4.20	<0.001	18.16	−11.16	<0.001
T5	25.74	−20.28	<0.001	−2.27	1.49	0.143	12.10	−9.76	<0.001
T6	21.12	−21.15	<0.001	−3.81	2.78	0.008	5.84	−5.28	<0.001
T7	14.01	−11.13	<0.001	−6.65	6.10	<0.001	0.08	−0.07	0.946

In Group II, a significant decrease in HR as compared to baseline was observed at T2, T6, and T7. At T4, a significant increase in HR was compared to baseline was observed. Maximum increase was 7.19% at T4 whereas maximum decrease was at T7 (−6.65%).

In Group III, a significant decrease in HR as compared to baseline was observed from T1 to T3, and a significant increase in HR as compared to baseline was observed from T4 to T6. Maximum decrease was observed at T3 (−10.45%) whereas maximum increase was observed at T4 (18.16%) [Table 5b].

Discussion

Laryngoscopy and intubation are common airway management methods undertaken during operative procedures to avoid respiratory depression leading to surgical emergency. Direct laryngoscopy and passage of endotracheal tube through the larynx are a noxious stimulus, which can provoke untoward response in the cardiovascular, respiratory, and other physiological systems.[15] Significant tachycardia and HTN can occur with tracheal intubation under light anesthesia. The magnitude of cardiovascular response is directly related to the force and duration of laryngoscopy.[16] The sympathetic response and the resulting hemodynamic response have been extensively studied and documented in different patient groups.[17] HTN, tachycardia, and arrhythmia caused by endotracheal intubation can be deleterious in patients with poor cardiovascular reserve. Such hemodynamic changes that occur during intubation may alter the delicate balance between myocardial oxygen demand and supply and precipitate myocardial ischemia in patients with coronary artery disease. Methods to attenuate these responses, both pharmacological and otherwise, have also been studied.[18-20]

With respect to SBP between administration of drugs (T0) and induction of anesthesia (T1), intergroup differences were not statistically significant. The time period between administration of drug and induction of anesthesia was too short to generate an effect. However, a statistically significant yet minor increase in SBP of patients in control group was observed (mean increase 1%). Thus, the attenuating effect of trial drugs on hemodynamics could be indirectly perceived. Just before intubation (T3), the three groups showed a significant intergroup difference with mean values in test groups being significantly lower as compared to control group. It was observed that at this point of time, mean SBP in both the test groups was lower as compared to that at baseline, whereas

in control group, it was higher as compared to that at baseline. This implied that the onset of action of both the drugs has initiated. Diltiazem reportedly is a rapid onset drug with onset time reported to be as low as 30–60 s[21] at a dose of 0.3 mg/kg; however, dexmedetomidine reportedly has an onset time of 5–8 min[22] at a dose of 0.1 ∝g/kg. Thus, calculating from the time of start of administration of drugs, the onset of action has taken place in both the drugs before intubation itself.

In the present study, for selecting the dose of diltiazem too, an emphasis on safety was made. IV diltiazem has been reported to be associated with increased incidence of nausea, slower ventricular rate, and hypotension;[23,24] hence, we targeted an optimum dose where side effects could be minimized. At lower dosages (0.2 mg/kg), some studies have shown to fail a suppressive effect of diltiazem;[23] however, a dose of 0.3 mg/ kg has reportedly been shown to be effective in attenuating the pressor response by a number of the studies.[25-27] Hence, this dosage was targeted to be used for the purpose of intervention in this study.

At baseline, it was ensured that all the patients in all the three groups were normotensive, had a normal pulse rate, and did not suffer from any respiratory abnormality compromising their ventilatory mechanism.

The test drugs were administered over a time of 10 min at the particular selected dosages before intubation and time gap between completion of administration of drug and intubation was kept at a maximum of 2 min. During this time period, the induction of anesthesia was also initiated.

By the time of intubation and thereafter, the trial drug groups had significantly lower mean value as compared to control group, thus showing that the antihypertensive effect of trial drugs helped to cope with the hemodynamic stress generated by laryngoscopy and intubation. As such, the percentage rise in SBP following intubation was 17.90% in control group as compared to 9.04% and 12.30%, respectively, in dexmedetomidine and diltiazem groups. As such, dexmedetomidine group showed a better attenuating effect as compared to diltiazem.

For DBP and MAP too, similar trends were obtained. For DBP following intubation, in control group, a rise of 19.96% was observed, whereas in dexmedetomidine and diltiazem groups, this rise was only 6.32% and 10.32%, respectively. The two trial groups tended to offset this rise too within 5 min after intubation and 1–2 min after the intubation, whereas in control group, the reflex sustained its effect even 5 min after intubation.

For MAP, the control group showed a rise of 19.04% following intubation as compared to 7.53% in dexmedetomidine and 11.14% in diltiazem groups. Within 5 min after intubation, both the trial groups were able to offset the pressor response, whereas in control group, though there was a decrease in MAP, the pressor response could not be completely suppressed. Here again, dexmedetomidine seemed to have a better as well as early response as compared to diltiazem.

In the present study, the maximum decrease in SBP was observed as 8.86% lesser in dexmedetomidine group as compared to control group just after intubation. Similarly, for DBP too, the mean blood pressure change in dexmedetomidine group was 13.64% lower as compared to control group. This could be attributed to blood pressure lowering property of dexmedetomidine. Dutta *et al* .'s[28] study showed that dexmedetomidine (0.3 □g/kg) as a single bolus IV dose and 10% lignocaine spray (1.5 mg/kg) given tracheally, both were effective in maintaining hemodynamic stability during extubation with respect to control. However, dexmedetomidine provided better attenuation of hemodynamic and airway responses than lignocaine, with smooth extubation and early neurological examination without any undue sedation and other side effects. For both blood pressure as well as HR, dexmedetomidine group showed a hemodynamic reflex suppressor ability, a finding supported by Yildiz *et al*.[29] The pattern of dexmedetomidine responses in the present study was similar to that reported by Menda *et al*.[30] who also showed that adjuvant use of dexmedetomidine provides successfully attenuates the hemodynamic response. In a study by Hanci *et al*.[31] while comparing the effects of fentanyl and dexmedetomidine in combination with propofol and lidocaine during tracheal intubation, bradycardia was cited to be the side effect associated with dexmedetomidine. However, in the present study, no such side effect was noticed, which mainly could be attributed to a lower dosage (0.5 □g/kg) in the present study as compared to a higher dosage (1 □g/kg) in the cited study. However, some other studies[32] have reported that HR is not dose dependent. In effect, the dose of dexmedetomidine used in the present study not only provided an attenuating response to hemodynamic reflex but also was safe.[30]. For diltiazem group, following intubation, mean increase in SBP was 5.6% lower as compared to control, whereas for DBP, this difference was 9.94%, thus indicating a suppressor and attenuating effect of diltiazem on the hemodynamic pressor response. A similar efficacy of diltiazem against placebo was observed by Nakao et al.,[33] who reported a significant attenuation of blood pressure and HR in diltiazem supplemented group as compared to controls. The trend of hemodynamic responses in the present study was similar to that shown by Mikawa et al.,[34] who also showed a before intubation gradual decline in hemodynamic parameters which enabled to suppress the pressor response to intubation. In another study, Singh et al. (2013)[35] showed that blood pressure changes following intubation were 10.5% lower in diltiazem group as compared to control whereas HR change was 23.44% lower in diltiazem as compared to control. In the present study, although blood pressure changes were somewhat similar, HR changes were lower yet not as low as shown by Singh et al.[35]

In the present study, dexmedetomidine at a dose of 0.5 □g/kg showed to have a better attenuation of pressor response as compared to diltiazem at a dose of 0.3 mg/kg. Although no direct study comparing the effect of two in a single study is available in literature, a number of studies independently have tested both the drugs against esmolol. In the present study, as far as HR was concerned, it was seen to be matched at baseline, but at subsequent intervals before intubation, dexmedetomidine group showed higher mean values as compared to the control and diltiazem groups. However, following intubation, it showed a minimum increase in HR (7.19%) as compared to control (31.67%) and diltiazem (18.16%), respectively. The benefit of using α-2 antagonists and CCBs is that they do reduce side effects such as nausea, vomiting, drowsiness, dry mouth, respiratory depression, histamine release and neuroexcitatory, and gastrointestinal effects as observed for opioids.[15-17] No other side effects such as nausea, vomiting, and dizziness were also noticed in the study. The findings in the present study were interesting, provided insights; however, as this was the first study comparing the efficacy of diltiazem to dexmedetomidine. There is no other empirical evidence available on the issue.

Hence, it is recommended that more evidence should be gathered to evaluate the efficacy of two drugs for hemodynamic pressor response attenuation as well as other parameters of interest before a clinical recommendation in favor of one of the two drugs could be formally made.

Conclusions

On the basis of above findings, it can be concluded that both dexmedetomidine and diltiazem were safe and effective in attenuating the hemodynamic response following laryngoscopy and endotracheal intubation; however, between two trial drugs, dexmedetomidine had a better response. Considering the lack of any previous empirical study, despite being logical, the results need to be corroborated in further studies to build a substantial clinical evidence.

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Conflicts of interest

There are no conflicts of interest.

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