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Original Article

Anaesthesia Section

Effect of Low Dose Intravenous Dexmedetomidine with 4% Sevoflurane on Haemodynamic Response during Laryngoscopy and Tracheal Intubation: A Randomised Controlled Study

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ABSTRACT

Introduction: Over the last decade, the use of dexmedetomidine has found favour in obtunding the haemodynamic response during laryngoscopy and tracheal intubation but the use of higher doses has lead to a number of adverse effects.

Aim: To compare the effect of low dose dexmedetomidine (0.5 µg/kg) and 4% sevoflurane (dial setting) with, Normal Saline (NS) and 4% sevoflurane (dial setting) on haemodynamic response to laryngoscopy and intubation.

Materials and Methods: This randomised double blind controlled study was carried out in 60 patients of American Society of Anaesthesiologists (ASA) class I, undergoing elective surgery under general anaesthesia. The patients were allocated to group DX (n=30) and group NS (n=30), who received dexmedetomidine 0.5 µg/kg infusion and NS infusion intravenous (i.v.) respectively, in equal volume over 10 minutes before anaesthesia induction. They were evaluated for the requirement of thiopentone sodium, vecuronium bromide and sevoflurane, total i.v. fluids transfused haemodynamic parameters intraoperatively (pre and post induction) and postoperatively at regular intervals, and side effects.

Results: On statistical comparison, Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) were found to be significantly less in group DX than in group NS with a p-value of <0.05. The total i.v. fluids infused in group NS and DX expressed as mean±Standard Deviation (SD) were 1145.00±228.21 and 1325.00±359.64, respectively. This was statistically significant. Thiopentone requirement was statistically more in group NS with a mean±standard deviation of 249.17±37.99 than in group DX (225.00±38.84). Similarly, sevoflurane requirement was statistically less in the DX group at various time intervals. Ten patients (33%) in group DX required antiemesis, compared to 13 patients (43%) in group NS. Two patients in group NS and three patients in group DX required injection (inj.) atropine to treat bradycardia.

Conclusion: On comparison, a combination of 4% sevoflurane with 0.5 µg/kg dexmedetomidine was more effective in attenuating pressor response than 4% sevoflurane (dial setting) alone, but is associated with minor and manageable risk of bradycardia and hypotension.

Keywords: Blood pressure, Endotracheal intubation, General anaesthesia, Heart rate

INTRODUCTION

Reflex response to laryngoscopy and endotracheal intubation, known as pressor response, causes acute changes in cardiovascular and cerebrovascular system [1]. These changes might be particularly catastrophic in patients who are vasoconstricted, volume depleted, or have severe cardiovascular and cerebrovascular diseases. The rise in BP and HR due to stimulation of laryngeal and pharyngeal tissues can be attributed to the increase in plasma catecholamines levels which peak in 30 seconds to 2 minutes. The magnitude of the pressor response depends on the force used during the procedure, duration of the procedure and the depth of anaesthesia during the procedure [2,3].

Various agents have been used to obtund it with variable success [4-11]. Intravenous dexmedetomidine decreases serum catecholamine levels by 90% when administered in the preoperative period, and thus blunts the haemodynamic response to laryngoscopy and tracheal intubation [12]. Most of these studies having used higher doses of dexmedetomidine (1–2 µg/kg) have reported various untoward effects including bradycardia and sedation [13-20]. At the same time, volatile anaesthetic agents like sevoflurane have shown to suppress the pressor response in combination with other agents [21].

Extensive search of literature did not reveal any study which had used a combination of low dose of dexmedetomidine (0.5 µg/kg body weight) and 4% sevoflurane (dial setting), to blunt the pressor response. Hence, this study was designed with an aim to compare the effect of low dose dexmedetomidine (0.5 µg/kg) and 4% sevoflurane (dial setting), with NS (normal saline) and 4% sevoflurane (dial setting) on haemodynamic response to laryngoscopy and intubation. The results of the study might help in avoiding the adverse effects of higher doses and concentration of these two drugs, while successfully blunting the haemodynamic response.

MATERIALS AND METHODS

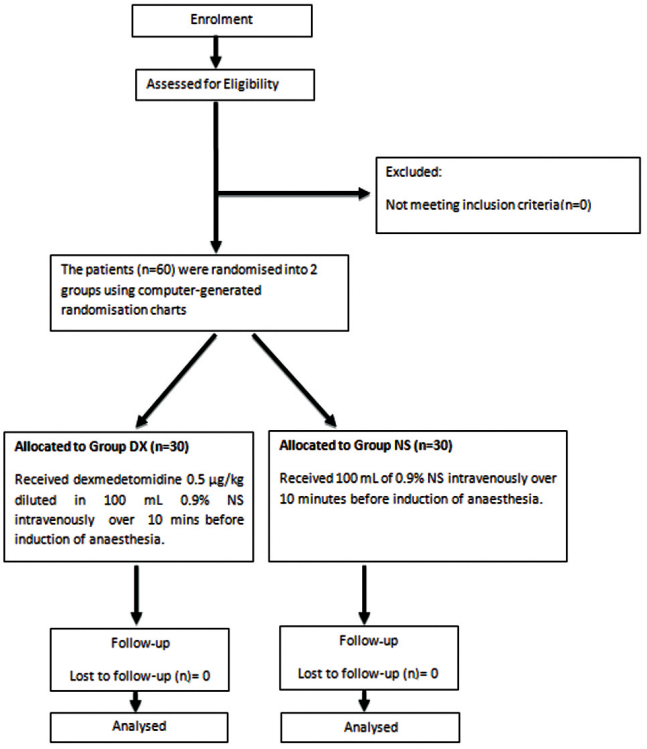
This randomised double blind controlled study was conducted in the Department of Anaesthesiology and Critical Care at University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, India, from December 2013 to April 2015. Institutional Ethical Committee (IEC) approval for the study was obtained on 27th November, 2013.

Inclusion criteria: All those patients were included who gave consent, were of either sex of age 18-60 years, ASA class I, airway Mallampatti grade I, scheduled for elective surgery under general anaesthesia.

Exclusion criteria: All those patients were excluded who had difficult airway, history of cardiovascular diseases, history of renal/hepatic/neurological/endocrine diseases, pregnant or lactating women, history of drug intake affecting cardiovascular parameters e.g.,

calcium-channel blockers, β-blockers, alpha blocker, magnesium sulphate, etc.

Sample size calculation: Considering a standard deviation of 31.3 and 37.3 in group dexmedetomidine and control respectively [22], to estimate a difference of 27 units in SBP after intubation at α=5% and power=80%, a sample of 26 cases was required in each group. So, after adding an attrition rate of 10-15%, the final sample size was 30 in each group. The patients were enrolled, assessed for eligibility and randomised as shown in the CONSORT flow diagram [Table/Fig-1].



[Table/Fig-1]: CONSORT flow diagram.
mL: Millilitres; NS: Normal saline; min: Minutes

Randomisation was carried out by an independent statistician not involved in the study using permuted blocks of varying sizes. This randomisation method ensured a balance in the number of patients allocated to each study group. The block sizes were multiples of two and were kept confidential. Group assignments within the block were determined [23]. After enrollment, group assignments were determined by a computer generated number sequence and were contained in sequentially numbered opaque envelopes to ensure blinding.

Blinding: The drugs were prepared as per the allocated group, and the syringes were coded by an independent anaesthesiologist not participating in the study, ensuring equal volume and colour. The patient and the observer were blind to the drug injected.

Study Procedure

Once the patient was in operation theatre, ASA standard monitoring was used and baseline parameters were recorded. After securing an i.v. line, infusion of ringer lactate was started. Patient then received either NS or dexmedetomidine infusion over a period of 10 min as per the group allotted. Anaesthesia was induced with inj.morphine 0.1 mg/kg (milligrams/kilograms) i.v. and inj.thiopentone sodium (2.5%) 3-5 mg/kg body weight i.v. till loss of eyelash reflex occurred and dose of thiopentone for loss of eyelash reflex was noted. Inj. vecuronium bromide 0.1 mg/kg i.v. was given after ensuring adequate bag and mask ventilation. Bag and mask ventilation with 50% nitrous oxide: oxygen mixture and 4% sevoflurane (dial setting) in oxygen was started and continued till complete relaxation was achieved. Relaxation was confirmed by Train Of Four (TOF) neuromuscular monitoring. Direct laryngoscopy and tracheal intubation with oral cuffed endotracheal tube of appropriate size was performed using Macintosh blade by an experienced anaesthesiologist and duration of laryngoscopy and intubation was recorded in seconds. Anaesthesia was maintained by using 50% nitrous oxide: oxygen mixture with sevoflurane in required dial concentration to maintain a Minimum Alveolar Concentration (MAC) of 1-1.5. IPPV (intermittent positive pressure ventilation) was used to maintain End Tidal Carbon Dioxide Concentration ($EtCO_2$) within 35±5 mmHg.

The TOF was used to assess the neuromuscular blockade and top up doses of vecuronium bromide 0.025 mg/kg were given accordingly. Normothermia was maintained by forced air warming devices and warm fluids. After the end of surgery, reversal of neuromuscular blockade was done by inj. neostigmine 0.05 mg/kg and inj.glycopyrrolate 0.005 mg/kg i.v. Extubation was done after adequate recovery.

If any patient showed hypotension (SBP ≤20% of the baseline value), it was initially managed by increasing the rate of i.v. fluids or giving additional fluid boluses and by decreasing the concentration of sevoflurane while maintaining the target MAC value. If patient did not respond to these measures, then it was managed by inj. ephedrine in boluses of 6 mg i.v., in the event of bradycardia (HR <20% of the baseline value), inj. atropine was given.

Primary outcome: Intraoperative haemodynamic parameters: HR and Non Invasive Blood Pressure (NIBP), SBP, DBP and MAP recorded at the following times:

- Before the infusion of study drug (baseline values);
- Every 5 minutes during the infusion;
- Before the induction of anaesthesia;
- Before intubation;
- After intubation at 1, 3, 5, 10 and 15 minutes;
- Every 15 minutes till 45 minutes.

Secondary outcomes:

- Oxygen Saturation (SpO_2) and $EtCO_2$- measured at the same intervals intraoperatively as BP and HR
- Concentration of sevoflurane (dial setting) required for maintenance- recorded with haemodynamic parameters at same time intervals intraoperatively.
- Requirement of thiopentone sodium and vecuronium bromide
- Postoperative haemodynamic parameters like HR and NIBP (SBP, DBP, and MAP) and sedation scores (using Ramsay Sedation Score)- recorded at every hour (hr) for three hours postoperatively.
- Adverse effects- like hypotension, bradycardia, Postoperative Nausea and Vomiting (PONV), dry mouth, shivering and sedation were recorded and treated appropriately.

Criteria used for withdrawal from study:

- Patients requiring more than 15 seconds for laryngoscopy and intubation.
- More than one attempt for laryngoscopy and intubation.

STATISTICAL ANALYSIS

Statistical analysis of parameters like patients' characteristics was done using Statistical Package for the Social Sciences (SPSS) version 17.0. Unpaired t-test was used to compare the data between the groups. Haemodynamic parameters between groups were analysed using repeated measures, two-way Analysis of Variance (ANOVA) followed by Tukey's test at 5% level of significance.

RESULTS

The patient demographics were comparable between the groups. The total i.v. fluids infused were significantly more and the thiopentone requirement was significantly less in the DX group with p-values of 0.023 and 0.018, respectively [Table/Fig-2].

Parameters	Group NS (n=30) Mean±SD	Group DX (n=30) Mean±SD	Unpaired t-test p-value
Age (years)	34.60±8.94	33.10±9.42	0.530
Body weight (kg)	54.90±5.63	56.03±9.20	0.568
Male:Female Ratio	1:4	1:2	-
Total duration of surgery (min)	90.50±44.65 (Range: 60-180)	110.00±54.40 (Range: 60-150)	0.135
Total duration of laryngoscopy and intubation (sec)	10.57±1.59 (Range: 6-14)	10.57±2.09 (Range: 8-15)	1.000
Total i.v. fluids infused (mL)	1145.00±228.21	1325.00±359.64	**0.023**
Thiopentone required (mg)	249.17±37.99	225.00±38.84	**0.018**
Vecuronium required (mg)	7.80±1.73	8.10±1.62	0.492

[Table/Fig-2]: Depicting demographics, surgical duration (min), duration of laryngoscopy and intubation (sec), total i.v. fluids infused (mL), dose of thiopentone and vecuronium required (mg) in the two groups.
p<0.05=Significant difference between groups

Since the duration of surgery was variable in all subjects of both groups, so for the purpose of statistical analysis, haemodynamic parameters were analysed for first 45 minutes in all cases. Comparison of haemodynamic parameters was done between the two groups at all the mentioned time intervals. HR was significantly less in group DX at various intervals as compared to group NS {at 10 minutes during drug infusion, before induction, before intubation, after intubation at 1, 3 and 5 minutes} [Table/Fig-3]. As shown in [Table/Fig-4], SBP before induction, before intubation and after intubation at 1, 3, 5 and 10 minutes was significantly less in DX group. Similarly, DBP was significantly lesser in group DX before intubation and after intubation at 1, 5 and 10 minutes [Table/Fig-5].The MBP was again less in group DX at 10 minutes during drug infusion, before induction, before intubation and after intubation at 1, 3, 5 and 10 minutes [Table/Fig-6]. Statistically significant differences in HR and SBP values were observed between the two groups till 45 minutes of administration of the drug infusion. DBP was reduced in both the groups from their baseline values till 15 minutes of drug infusion, and the difference between the groups was significant till 45 mins. The requirement of sevoflurane was statistically less in group DX with a p-value of 0.028 [Table/Fig-7].

Time interval		Group NS (n=30) Mean±SD	Group DX (n=30) Mean±SD	ANOVA and Tukey's test p-value
Before medication		85.27±10.75	85.70±9.56	
Drug Infused	0 min	87.00±10.90	84.60±9.41	
	5 min	85.90±11.30	79.30±8.94	**0.024**
	10 min	85.90±10.28	76.93±8.68	
Before induction		86.10±11.17	76.43±8.05	
Before intubation		78.90±10.80	72.93±8.83	
After intubation 1 min		102.27±11.91	90.53±12.39	
3 min		94.27±11.98	83.40±9.47	
5 min		88.10±10.40	77.93±7.50	
10 min		82.30±10.33	73.33±9.89	**<0.001**
15 min		80.57±10.29	73.40±10.04	
30 min		78.83±9.22	75.80±11.02	
45 min		80.73±7.96	76.37±9.51	
Postoperative	0 h	86.10±11.17	80.13±11.58	
	1 h	77.37±9.40	76.50±8.65	
	2 h	77.07±6.98	76.67±7.09	0.118
	3 h	77.50±8.28	77.87±6.83	

[Table/Fig-3]: Showing Heart Rate (bpm) with p-value in two groups at varying time intervals using two-way ANOVA followed by Tukey's test.
p-value <0.05 statistically significant

Time interval		Group NS (n=30) Mean±SD	Group DX (n=30) Mean±SD	ANOVA and Tukey's test p-value
Before medication		120.73±5.87	119.67±6.35	
Drug Infused	0 min	126.17±6.84	122.77±6.40	
	5 min	120.77±6.54	117.23±5.71	**0.02**
	10 min	119.40±6.15	114.03±6.41	
Before induction		118.30±7.04	111.20±7.30	
Before intubation		94.53±9.06	82.27±9.01	
After intubation 1 min		118.27 ±11.15	103.17±13.32	
3 min		110.30±9.98	100.83±11.19	
5 min		106.03±9.21	95.70±6.67	
10 min		103.67±6.98	94.97±7.43	**<0.001**
15 min		108.30±8.57	100.73±8.71	
30 min		112.40±9.31	110.03±10.87	
45 min		114.17±8.51	109.53±10.24	
Postoperative	0 h	120.83±2.47	117.90±8.07	
	1 h	117.70±8.18	114.83±8.73	
	2 h	117.37±7.04	113.13±6.87	0.06
	3 h	119.43±6.42	115.63±6.00	

[Table/Fig-4]: Depicting Systolic blood pressure (SBP) (mmHg) in two groups at varying time intervals.
p-value <0.05 statistically significant

Time interval		Group NS (n=30) Mean±SD	Group DX (n=30) Mean±SD	ANOVA and Tukey's test p-value
Before medication		78±8.64	78.83±7.29	
Drug Infused	0 min	79.90±8.00	79.23±7.56	
	5 min	78.60±8.54	77.43±7.38	0.205
	10 min	78.77±7.50	74.97±7.11	
Before induction		77.60±9.42	71.10±9.07	
Before intubation		61.57±8.57	50.93±9.08	
After intubation 1 min		79.00±10.82	69.23±14.35	
3 min		71.60±10.81	65.90±12.03	
5 min		69.97±9.33	60.53±8.68	
10 min		68.10±8.52	60.60±9.84	**0.009**
15 min		68.50±11.18	66.70±12.00	
30 min		73.83±11.29	75.23±14.00	
45 min		72.80±10.46	73.70±12.51	
Post-operative	0 h	73.63±11.08	73.47±10.06	
	1 h	73.87±9.87	71.10±11.42	
	2 h	75.50±8.54	72.33±10.62	0.107
	3 h	77.27±8.32	75.03±9.84	

[Table/Fig-5]: Showing Diastolic Blood Pressure (DBP) (mmHg) in two groups at varying time intervals.
p value <0.05 statistically significant

Desaturation and overt sedation was reported in none of the patients in either group. PONV was observed in 33% of the patients in group DX, as compared to 43% in group NS. Hypotension was observed in 76.67% patients in group DX, as compared to 23.33% patients in group NS. Two patients in group NS and three in group DX developed bradycardia intraoperatively which required inj. Atropine.

DISCUSSION

In the present study, a low dose 0.5 µg/kg dexmedetomidine was used in combination with 4% sevoflurane (dial setting), and it was hypothesised that the drug combination would better attenuate the pressor response compared to NS and 4% sevoflurane, without causing significant adverse effects.

Time interval		Group NS (n=30) Mean±SD	Group DX (n=30) Mean±SD	ANOVA and Tukey's test p-value
Before medication		91.77±6.76	93.03±6.38	
Drug Infused	0 min	95.53±6.46	93.53±6.07	
	5 min	91.60±7.05	90.43±6.12	**<0.001**
	10 min	91.53±6.00	88.07±6.19	
Before induction		92.13±7.25	84.60±7.57	
Before intubation		72.67±8.55	61.90±8.40	
After intubation 1 min		93.03±10.31	81.47±12.15	
3 min		86.17±9.35	78.63±11.18	
5 min		82.23±8.15	72.37±6.99	
10 min		80.53±7.84	72.30±8.63	**<0.001**
15 min		83.27±9.17	78.60±10.50	
30 min		87.23±9.03	87.47±11.50	
45 min		86.83±8.64	85.73±10.69	
Post-operative	0 h	89.73±9.60	89.50±8.99	
	1 h	89.10±8.52	86.63±9.15	0.062
	2 h	89.70±7.08	87.00±8.92	
	3 h	91.90±6.01	88.87±8.12	

[Table/Fig-6]: Showing Mean arterial blood pressure (MBP) (mmHg) in two groups.
p value <0.05 statistically significant

Time interval	Group NS (n=30) Mean±SD	Group DX (n=30) Mean±SD	Unpaired t-test p-value
After intubation 1 min	2.83±0.98	2.20±0.88	
3 min	2.00±0.45	1.50±0.50	
5 min	1.53±0.62	1.23±0.50	
10 min	1.47±0.62	1.17±0.46	**0.028**
15 min	1.37±0.55	1.13±0.43	
30 min	1.30±0.46	1.53±1.85	
45 min	1.33±0.47	1.23±0.43	

[Table/Fig-7]: Showing sevoflurane concentration (%) required in two groups.
p value <0.05 statistically significant

The total i.v. fluids infused in group DX were significantly more than that in group NS as depicted in [Table/Fig-2] (p-value of 0.023). This can be explained by the vasodilating effects of dexmedetomidine, requiring more fluid administration in order to maintain the BP. The dose of thiopentone sodium required for the induction of anaesthesia was significantly lower in group DX as compared to group NS (p-value of 0. 018). This finding in the study further supports the findings of Bajwa SJ et al., and Saraf R et al., who used higher doses of 1 µg/kg and 0.6 µg/kg of dexmedetomidine, respectively before induction of anaesthesia and observed significant reduction in dose requirements of thiopentone sodium [18,24]. Similar results were obtained by other authors also [13,17]. It can be inferred from the results of the present study that even low dose of dexmedetomidine 0.5 µg/kg has an anaesthetic sparing effect on thiopentone sodium.

It was observed in the present study that the total vecuronium requirement was similar in both the groups and our results were similar to the observations of Lawrence CJ and De Lange S [13]. Saraf R et al., reported significant reduction in dose of vecuronium after using dexmedetomidine 0.6 µg/kg i.v. [24]. However, they did not mention the average duration of surgery in both the groups.

As shown by [Table/Fig-3], in group DX, HR decreased during infusion of dexmedetomidine and before induction from the baseline value. In accordance with these results, Lawrence CJ and De Lange S and Sağıroğlu AE et al., also reported fall in the HR during the drug infusion of dexmedetomidine [13,25]. Before intubation, there was transient fall in HR in NS group, which can be explained by higher thiopentone requirement in the group. At 1 minute, 3 minutes and 5 minutes of tracheal intubation, HR difference between two groups was significant (p-value of <0.001). In group DX, the HR was low at all the points of time as compared to group NS.

The statistical comparison in terms of SBP between two groups revealed a significant difference before induction (following medication), before intubation (following induction) and at 1, 3, 5 and 10 minute following intubation with group DX having lower SBP values [Table/Fig-4]. Similar results were obtained when MBP was compared between the two groups [Table/Fig-6]. Significantly, lower DBP values were observed before intubation, after intubation at 1,5 and 10 minutes (p-value of 0.009) in DX group compared to NS group [Table/Fig-5]. This can be explained by the fact that both sevoflurane and dexmedetomidine cause vasodilatation, and reduce peripheral vascular resistance.

Hence, both groups showed successful attenuation of pressor response. Results of the present study were similar to those obtained by Saraf R et al., Tomiyasu S et al., and Muñoz HR et al., [24,26,27]. However findings of the present study were in contrast to those obtained by Sağıroğlu AE et al., who demonstrated that dexmedetomidine in the dosage of 0.5 µg/kg i.v. caused significant increase in SBP at 1, 3, 5 and 10 minutes after intubation as compared to dexmedetomidine 1 µg/kg i.v. [25].This difference in the results can be explained by the use of 4% sevoflurane along with dexmedetomidine in the present study.

The requirement of sevoflurane concentration for maintenance was based on SBP in order to maintain it within±20% of baseline values (before medication) of the respective group. After tracheal intubation at 1 minute, significantly higher concentration of sevoflurane was required in group NS as compared to group DX (2.83±0.98 vs 2.20±0.88). After intubation at 3 minutes and onwards there was a significant reduction in the requirement of sevoflurane in both the groups. But the requirement in group DX was lower as compared to group NS at every point of time till 45 minutes and statistical analysis showed an overall significant difference in sevoflurane concentrations required by two groups with a p-value of 0.028 [Table/Fig-7]. These results were similar to Lawrence CJ and De Lange S; Keniya VM et al., and Bajwa SJ et al., [13,17,18].

None of the patients in either group in the present study showed desaturation (SpO_2 <94%) at any time interval and all patients were arousable and calm with a Ramsay sedation score of 2 in the immediate postoperative period. These findings were similar to those observed by Saraf R et al., [24]. All patients of both groups were observed for PONV and were treated with inj. ondansetron 0.1 mg/kg i.v. if required. The requirement of antiemetic in group DX was lower (10 patients, 33%) than in group NS (13 patients, 43%).This was similar to the results obtained by Lawrence CJ and De Lange S who attributed this to the reduced salivation and gastrointestinal motility due to the alpha-2 agonist action of dexmedetomidine [13].

Hypotension was noted in more patients in group DX (23 patients, 76.67%) than group NS (7 patients, 23.33%). It was treatable with additional fluid boluses and no patient in either group required inj. ephedrine. Two patients in group NS and three in group DX required inj. atropine to treat bradycardia intraoperatively. This was similar to the results observed by other authors [13,28]. In contrast to the findings of the present study, Sağıroğlu AE et al., used 0.5 and 1 µg/kg dexmedetomidine and did not find hypotension or bradycardia in either group [25].This may be because they conducted the study for only 10 minutes following tracheal intubation. However, Saraf R et al., used 0.6 µg/kg dexmedetomidine and observed significantly higher incidence of hypotension and bradycardia with dexmedetomidine [24].

Limitation(s)

Opioids were used in all the patients at the time of induction which could have blunted the haemodynamic response to laryngoscopy and intubation. Secondly, the study considered only ASA I patients hence the usefulness of dexmedetomidine in high risk patients could not be evaluated. Thirdly, this study was done at a single

centre and the plasma catecholamine levels at laryngoscopy and intubation could not be quantified.

CONCLUSION(S)

The results of present study conclude that haemodynamic responses induced by laryngoscopy and tracheal intubation can be better attenuated by a combination of low dose dexmedetomidine 0.5 µg/kg and 4% sevoflurane as compared to 4% sevoflurane alone, although the combination was associated with minor risk of bradycardia and hypotension, which was easily manageable with intravascular fluid boluses. On comparing the anaesthetic requirements between the groups, dexmedetomidine group had an anaesthetic sparing effect as it resulted in less thiopentone and sevoflurane requirements at induction and during intraoperative period respectively. Large scale multicentre studies are recommended to study the utility of dexmedetomidine infusion or low dose bolus doses to blunt haemodynamic response to intubation in high risk patients.

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