Effect of dexmedetomidine on hemodynamic responses during tracheal extubation

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Abstract

Introduction and Aims: Dexmedetomidine, an α-2-adrenoreceptor agonist, offers excellent sedation without significant effect on respiratory or cardiovascular stability. It may be, thus, helpful to achieve smooth extubation.
This study was conducted to assess the efficacy of dexmedetomidine in attenuating hemodynamic responses and airway reflexes encountered during extubation.
Materials and Methods: Sixty ASA I & II patients, aged 18-50 years, undergoing elective surgery under general endotracheal anesthesia were enrolled for the study. They were assigned to two groups-1 and 2, of 30 patients each, in a randomized, double blind manner, to receive dexmedetomidine or normal saline (NS) intravenous infusion, respectively. Hemodynamic parameters (heart rate, systolic, diastolic and mean arterial pressures) were recorded at the time of starting the study drug infusion, during the infusion, at extubation and thereafter at specific intervals for 30 minutes. Quality of extubation was assessed on a 5-point scale; postoperative sedation assessed by Ramsay Sedation Scale. Any untoward occurrence like undue sedation, vomiting, hypotension, respiratory depression, laryngospasm, bronchospasm and desaturation was noted.
Results: Heart rate, systolic, diastolic and mean arterial pressures were significantly higher in Group 2 ($p < 0.05$). Group 1 patients (those receiving dexmedetomidine) had smoother extubation and were calm and peaceful at extubation as well as post-extubation when compared to Group 2.
Conclusion: Dexmedetomidine 0.5 mcg/kg infusion given over 10 minutes prior to extubation, decreases hemodynamic responses and results in smooth extubation.

Keywords : α-2-adrenoreceptor agonist, Dexmedetomidine, General anesthesia, Extubation, Hemodynamics.

Introduction

The primary goal of an anesthesiologist is to maintain a patent airway during general anesthesia.[1] In 1921, Ivan W. Magill and Rowbotham introduced endotracheal intubation and since then, it has become an essential component of balanced anesthesia to secure the airway as well as isolate and protect it. Endotracheal intubation is found to be associated with cardiovascular and airway responses.[2] Emergence from general anesthesia and extubation are likewise, accompanied by hemodynamic and airway responses resulting in arterial hypertension, tachycardia, and dysrhythmias. Often, there are marked increases in blood pressure and heart rate at the time of 'light' extubation.[3,4]

It has been suggested that tracheal extubation also produces unfavorable hemodynamic alterations which may compromise myocardial oxygenation in the postoperative period.[5] Tracheal extubation has been found to be associated with respiratory complications three times more commonly than tracheal intubation and induction of anaesthesia (4.6 vs 12.6%).[6]

Tracheal intubation as well as extubation, are associated with hemodynamic responses like increases in heart rate, blood pressure, myocardial contractility and systemic vascular resistance. This is the result of increased concentration of plasma catecholamines, which, in turn, is caused by raised sympathoadrenal activity.[7,8] These responses may be tolerated by most patients without much clinical consequences,[9] but not so by patients with diseases like hypertension, ischemic heart diseases, pheochromocytoma, hyperthyroidism, diabetes and pregnancy-associated-hypertension.

Thus, it would be rational to protect against these hemodynamic responses to extubation in order to avoid these complications. To overcome these undesirable responses, multiple pharmacological and non-pharmacological strategies that minimize the hemodynamic adverse responses have been studied.[10]

Dexmedetomidine, a comparatively newer drug, shows a high ratio of selective α-2 receptor activity (α2/α1 1600:1), making it a complete α-2 agonist. It possesses sedative, anxiolytic and analgesic actions, but does not significantly affect patient arousability and respiratory function. Studies suggest that it can attenuate stress response to intubation in a dose-dependent manner.[11] However very few studies are available with regard to attenuation of hemodynamic response to extubation using dexmeditomidine.

This study was conducted to assess the efficacy of dexmedetomidine infusion, 0.5µg/ kg body weight, administered prior to extubation, in attenuating the hemodynamic responses and airway reflexes associated with reversal and extubation. Side effects of the drug, if any, were recorded.

Materials and Methods

After obtaining approval from the Institutional Ethics Committee, a hospital-based, double blind, randomized,

controlled study was carried out to study the efficacy of dexmedetomidine in attenuation of hemodynamic response during tracheal extubation. Applying consecutive sampling technique, 60 patients of either sex, belonging to ASA physical grades I & II, 18-50 years old, posted to undergo surgery under general anesthesia, were enrolled for the study. Patients with co-morbidities like cardiovascular or respiratory diseases, diabetes, obesity, hypertension, and those taking medications that have an effect on the cardiovascular system were not included in the study. Pregnant patients and currently lactating women were also excluded from the study. Other exclusion criteria included difficult airway, history of sleep apnea and patients taken up for emergency procedures.

The patients were then randomly assigned to two groups (30 in each group) using computer generated random numbers to receive injection dexmedetomidine or Normal saline (NS).

Strategy: This was a double blinded study i.e. the patient as well as the investigator (anaesthesiologist recording the data) were blinded and hence, were unaware of the group the patient belonged to. Patients were interviewed and examined one day before surgery. Thorough preoperative assessment and relevant investigations as per case record form (complete blood count, liver function tests, renal function tests, blood sugar, ECG and X-ray chest) were done. No hypnotic medications were given to the patients on the night before surgery.

On the morning of surgery, after taking written informed consent, patients were shifted to the operation theatre. Standard ASA (American Society of Anesthesiologists) monitors were attached to record vital parameters like Electrocardiography (ECG), Oxygen saturation (SpO_2), Non-invasive blood pressure (NIBP) and End-tidal carbon-dioxide ($EtCO_2$). Baseline parameters were recorded. Intravenous (IV) access was secured with a 20G cannula and an infusion of Ringer's lactate, at the rate 10-15ml/kg, was started.

Patients were preoxygenated with 100% oxygen for 3min and premedicated with injection glycopyrolate 0.2mg, injection ondansetron 4mg, injection midazolam 1mg and injection fentanyl 2µg/kg intravenously.

They were induced with injection thiopentone sodium 4-5mg/kg or injection propofol 2mg/kg IV and neuromuscular blockade was achieved with injection atracurium besylate 0.75mg/kg or injection vecuronium bromide 0.1mg/kg IV. Laryngoscopy was done after 3mins of giving muscle relaxant and intubation achieved with 8.0 - 8.5mmID cuffed endotracheal tube for males and 7.0 - 7.5mmID for females. Correct placement of the tube was confirmed by auscultation and square wave capnography.

Anesthesia was maintained with a mixture of nitrous oxide: oxygen (50:50) with isoflurane (0.8- 1.2%) and incremental doses of inj. atracurium/ inj. vecuronium, using closed circuit with mechanical ventilation while maintaining the $EtCO_2$ within normal limits.

Twenty minutes prior to the expected time of extubation, isoflurane was discontinued and patients were randomly allocated to one of the following two groups in a double blind manner. The study drugs, either dexmedetomidine or Normal saline were given according to the group allocation.

Group 1 (n = 30): received a bolus of IV dexmedetomidine, 0.5µg /kg body weight, diluted to 20 ml with NS, over 10 minutes with the help of a syringe pump and

Group 2 (n = 30): received IV Normal Saline 20 ml, over 10 minutes with a syringe pump.

The time of starting the study drug was recorded. Heart rate, systolic, diastolic and mean arterial blood pressure, and oxygen saturation (SpO_2) were noted prior to infusion and at 1min, 3min, 5min, 7min and 10 minutes after starting infusion of the study drug / normal saline.

At the termination of the study drug infusion, nitrous oxide was discontinued. When patients regained adequate spontaneous respiratory efforts, the remaining neuromuscular blockade was reversed with inj. neostigmine 0.05mg/kg and inj. glycopyrrolate 8µg/kg IV. Oropharyngeal secretions were cleared by gentle suction. Above mentioned hemodynamic parameters and SpO_2 were again recorded at the time of reversal.

Patients were extubated, on fulfilling the extubation criteria, which are, as follows:[12]
1. Sustained head lift for more than 5 seconds.
2. Sustained hand grip for more than 5 seconds.
3. Adequate level of consciousness.
4. Maximum inspiratory pressure ≥ 40 to 50 cm H_2O.

A 5-point scale was used to rate quality of extubation, as follows:
1. No coughing
2. Smooth extubation, minimal coughing
3. Moderate coughing (3 or 4 times)
4. Severe coughing (5 to 10 times) and straining
5. Poor extubation, very uncomfortable (laryngospasm and coughing >10 times)

Other criteria noted were:

Time to eye opening i.e. interval between cut-off of nitrous oxide to eye opening.

Time to extubation i.e. the interval between cut-off of nitrous oxide to extubation.

Occurrence of number of coughs per patient was recorded for 15mins post-extubation. Any untoward effects like laryngospasm, bronchospasm or desaturation over a period of 15mins following extubation were noted.

Above monitoring parameters HR, SBP, DBP, MAP and SpO_2 were recorded again after extubation, and at 1min, 3mins, 5mins, 7mins, 10mins, 13mins and 15mins after extubation.

After extubation, quality of sedation was assessed by Ramsay Sedation Scale, as given below:[13]
1. Anxious and agitated, restless.
2. Co-operative, oriented, tranquil.
3. Responsive to verbal commands, drowsy.
4. Asleep, responsive to light stimulation.
5. Asleep, slow response to stimulation.
6. No response to stimulation

Possible adverse effects such as bradycardia, tachycardia, arrhythmias, hypotension, hypertension, vomiting and dry mouth during the administration of dexmedetomidine infusion and in the postoperative period, were recorded and treated as follows:

Bradycardia (HR<45/min): inj. atropine (0.5mg IV)

Tachycardia (HR ≥ 160/min, lasting longer than 3min): Beta (β) blockers –inj. metoprolol IV, in titrated dose.

Hypotension (decrease in diastolic pressure >25% of the baseline, or an absolute systolic value <90mmHg): IV fluids; if not controlled within 3min by fluids – inj. ephedrine (5-10mg IV bolus).

Hypertension (defined as SBP >180mmHg, lasting longer than 3min): inj. nitroglycerine

Pain was assessed every 3min for 15mins, according to Visual Analogue Scale (VAS). Rescue analgesia was provided with inj. paracetamol.

VAS Score

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0              3              5              7              10
↑_____↑_____↑_____↑_____↑
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0 - no Pain
1-3 - mild Pain
4-7 - moderate Pain
>7 - severe Pain
10 - worst Pain

Patients were shifted to recovery room and all the above parameters were monitored for 15-20 min.

Ethical Justification and Statistical Analysis

Ethical clearance for conducting the study was obtained from the Ethics Review Committee of the institute. This study was ethically justified as all the drugs used in management of patients for general anesthesia are described in the available literature and universally dispensed to such patients.

The sample size was calculated by taking assistance from the statistician, based on literature data*. In the study report, the extubation, awakening, and orientation times in patients who received dexmedetomidine or fentanyl data are expressed as Mean ±SD. The extubation time (min) which is distributed in both Dexmedetomidine and Fentanyl groups is 7.55 ± 4.03 and 5.61 ± 3.57 respectively (table-iv). Here, we considered the more variation value, 4.03. When we used minimum 80% power value and 5% level, the required sample size was 55 and when using 85% power value and 5% level, then required sample size was 62.Hence, we took the sample size for the above study as 60, divided into 30 per group.

Thus, required sample size for this study: 30+30=60

Use of statistical software to calculate sample size = SAS 9.1.3

*Reference Article: "Comparison of the Effects of Dexmedetomidine Versus Fentanyl on Airway Reflexes and Hemodynamic Responses to Tracheal Extubation During Rhinoplasty: A Double-Blind, Randomized, controlled Study" by Recep Aksu, MD; Aynur Akın, MD; Cihangir Bicer, MD; Aliye Esmaoglu, MD; Zeynep Tosun, MD; and Adem Boyacı, MD Department of Anesthesiology, Erciyes University School of Medicine, Kayseri, Turkey, Current Therapeutic Research, vol-70, number 3, June 2009. Current Therapeutic Research

Data was analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). We used the Chi square test or Fisher's exact probability test for categorical data and Student's t test for continuos data. A p-value < 0.05 was considered to be statistically significant.

Results

60 patients posted for surgery under general anesthesia were randomly assigned to two groups (n=30) as follows and were observed to study the effect of IV dexmedetomidine for attenuation of hemodynamic responses and airway reflexes associated with extubation.

Group 1 received 0.5µg /kg body weight bolus of dexmedetomidine, diluted to 20 ml in Normal saline, intravenously over a period of 10 minutes with the aid of a syringe pump whereas Group 2 received Normal saline, 20 ml, over 10 minutes with syringe pump.

All the patients in both the groups were matched in terms of age, sex, ASA physical grade and weight of the patients.

The patients were comparable in terms of ASA grade (p=1.00). [Table 1]

All the patients in both the groups were in the age group of 18 - 50 years. The mean age of patients in Group 1 was 32.50 ± 9.41 years; in Group 2, it was 31.50 ± 9.65 years (p =0.6860). [Table 2[

Heart rate at the start of the study drug infusion (0 min-SD-HR) was taken as baseline for intra-group comparison of both groups. Prior to infusion (T0), heart rate in Group 1 (85.23) and in Group 2 (83.23) was comparable (p=0.2953). After 5, 7 and 10mins of drug infusion, there was significant decrease in the heart rate in Group 1; whereas in Group 2, heart rate rose constantly from the baseline value (p=0.001). Post-extubation, at 15min (T13), the heart rate returned to baseline in Group 1, whereas in Group 2, it continued to be above the baseline. This was statistically significant (p value <0.0198). [Graph 1]

There was a notable fall in both, the systolic and diastolic blood pressure from baseline in Group 1 (blood pressure values at 5,7 and 10 minutes of infusion of drug as

well as post-extubation) whereas, blood pressure values in control group were observed to be rising above baseline and these observations were statistically significant (p value <0.05).[Graph 2,3]

Mean arterial pressure in Group 1 remained below baseline value (5%-6%) throughout the study period, whereas in Group 2 mean blood pressure remained above the baseline value (6%-18%), and this difference was statistically significant (p value <0.05). [Graph 4]

There was significant prolongation of both 'Time to eye opening' and 'Time to extubation' in Group 1 as compared to Group 2 (p<0.0001). The occurrence of number of bouts of cough per patient was significantly lesser in Group 1

(0.46 ± 0.17) as compared to Group 2 (1.60 ± 1.10) (p<0.0001).

Group 1 patients had a smoother extubation as indicated by a lower score on the 'Extubation quality 5-point scale' compared to Group 2 [Table 3].

On assessment of the patients in the two groups by Ramsay Sedation Scale, patients receiving dexmedetomidine were found to be calm, peaceful, sedated but rousable at extubation and also post-extubation at 3,5,7,10,13 and 15 minutes [Table 4]. In comparison, patients in the control group were cooperative and oriented but restless.

Table 1: Distribution of ASA grading in the two groups studied.

ASA Grade	Group 1 (Dexmeditomidine)		Group 2 (Normal Saline)	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
Grade I	24	80	22	73.33
Grade II	06	20	08	26.67
Total	30	100	30	100

p value =1.00

Table 2: Distribution of age in two groups.

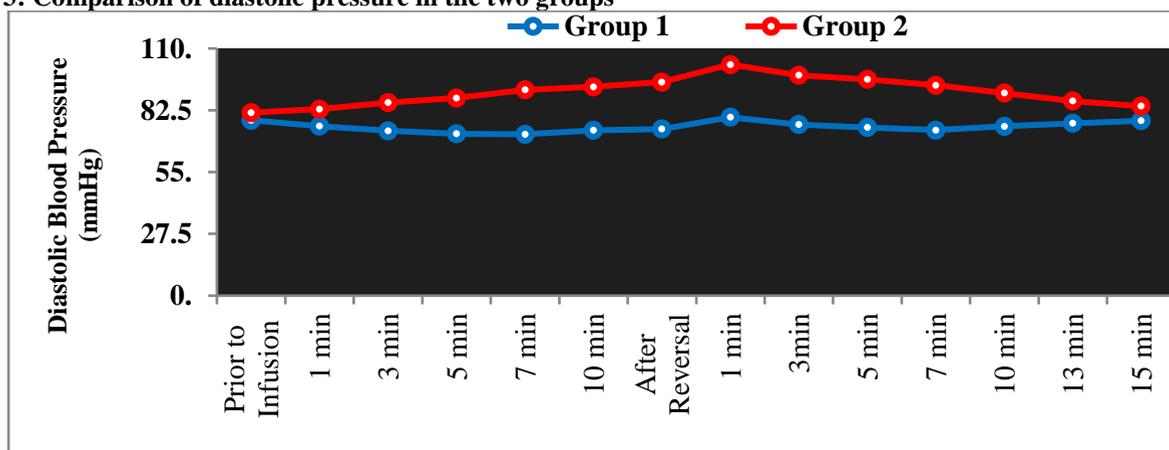| Age (years)	Group 1(Dexmeditomidine)		Group 2 (Normal Saline)	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)
18-20	02	6.67	03	10
21-30	14	46.67	14	46.67
31-40	08	26.67	06	20
41-50	06	20	07	23.33
Total	30	100	30	100
Mean ± S.D.	32.50 ± 9.41		31.50 ± 9.65	

p value = 0.6860

Graph 1: Comparison of heart rate in two groups
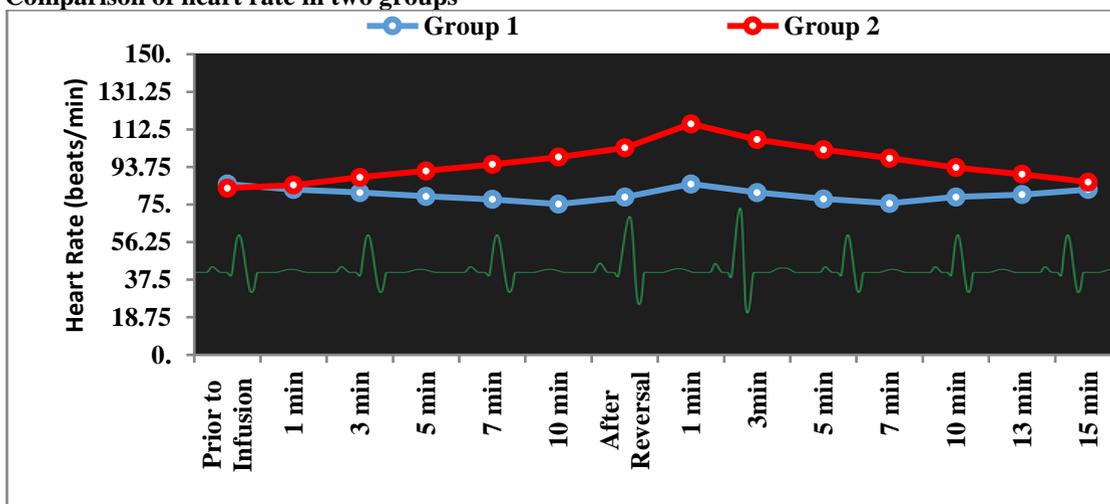
Graph 2: Comparison of systolic blood pressure in two groups
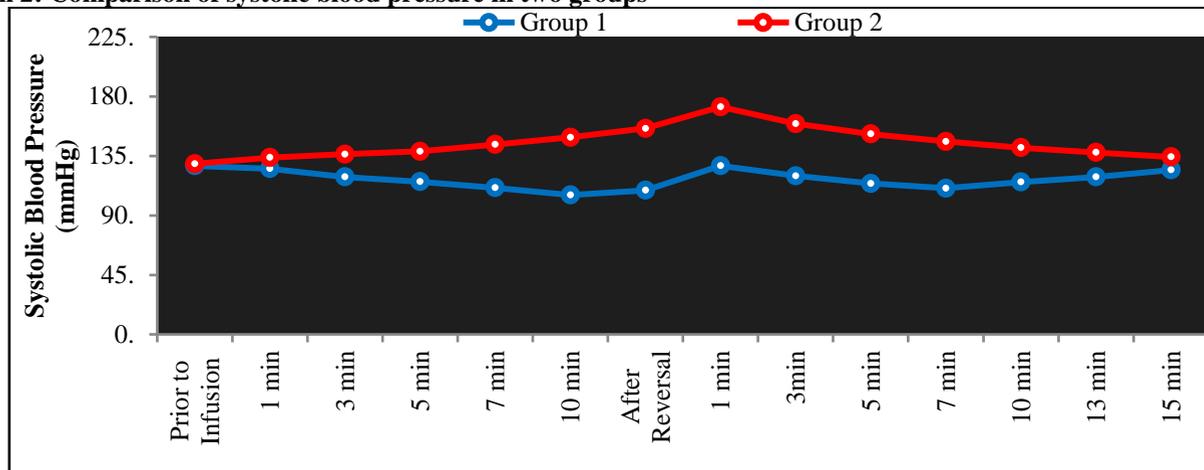
Graph 3: Comparison of diastolic pressure in the two groups

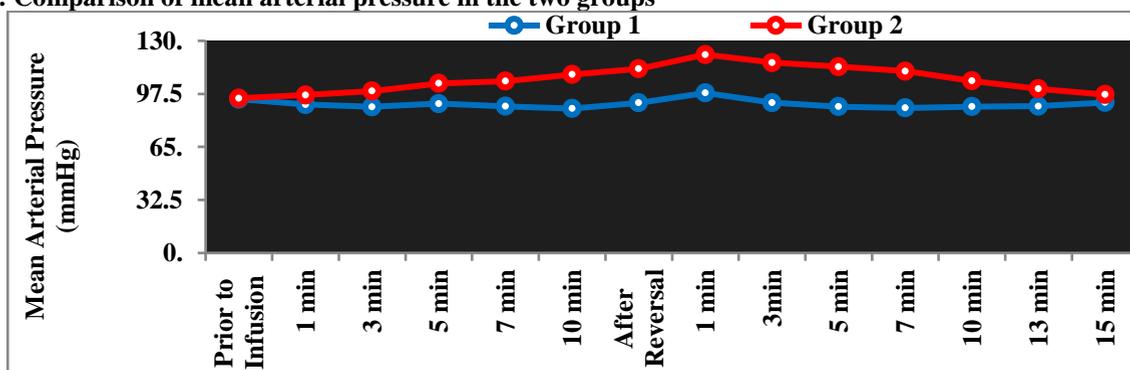**Graph 4: Comparison of mean arterial pressure in the two groups**

Table 3: Comparison of extubation parameters in two groups studied

	Group 1 (Dexmeditomidine)	Group 2 (Normal Saline)	*p*-value
Time to extubation (in mins)	18.27 ± 2.20	14.57 ± 1.89	<0.0001
Time to eye opening (in mins)	17.73 ± 1.74	13.70 ± 1.70	<0.0001
Extubation quality 5-point scale	1.07 ± 0.25	1.57 ± 0.73	<0.0008
No. of bouts of cough/patient	0.46 ± 0.17	1.60 ± 1.10	<0.0001

Table 4: Comparison of Ramsay sedation scale in two groups studied.

	Ramsay Sedation Scale	Group 1 (Dexmedetomidine)	Group 2 (Normal saline)	*p* value
P1	Post-extubation at 1min	2.10 ± 0.31	1.00 ± 0.00	<0.0001
P2	Post-extubation at 3min	2.13 ± 0.35	1.07 ± 0.25	<0.0001
P3	Post-extubation at 5 min	2.20 ± 0.31	1.03 ± 0.18	<0.0001
P4	Post-extubation at 7 min	2.00 ± 0.00	1.03 ± 0.18	<0.0001
P5	Post-extubation at 10 min	2.00 ± 0.00	1.00 ± 0.00	<0.0001
P6	Post-extubation at 13 min	2.10 ± 0.31	1.03 ± 0.18	<0.0001
P7	Post-extubation at 15 min	2.00 ± 0.00	2.03 ± 0.18	0.3651

Discussion

Emergence from general anesthesia and tracheal extubation are often accompanied with stress responses like tachycardia, hypertension and bronchospasm. Hartley M and Vaughan RS found that heart rate and systolic blood pressure increased by 20% during extubation and the cause for this was attributed to increased plasma concentration of adrenaline.[4] This increase in hemodynamic parameters may predispose susceptible patients to myocardial ischemia or infarction. Extubation is associated with increased sympathetic stimulation, which results in marked increases in heart rate and blood pressure. Alpha-2(α-2) agonists like dexmeditomidine may help to minimize this sympathetic outflow and thus, may counteract the hemodynamic fluctuations caused in response to extubation.[14] Hence, we conducted a randomized double-blind controlled study to evaluate the use of dexmeditomidine (when compared to Normal saline) in attenuating the hemodynamic responses and airway reflexes caused by extubation.

In our study, mean heart rate of the patients, which was comparable for both the groups at baseline, showed a rising trend in Group 2(control group). There was significant rise in heart rate from baseline immediately after reversal and following extubation; after extubation, too, the heart rate remained higher. In Group 1(dexmeditomidine group), there was no rise in heart rate; instead, the heart rate fell below the baseline following the initiation of dexmedetomidine infusion and it remained at baseline thereafter (Graph 1). This observation is comparable with the study done by Jain D et al.[14] They observed a marked fall in the pulse rate 7-10 minutes after the start of dexmedetomidine infusion (p<0.05) and it continuosly remained below the baseline following extubation also. On the other hand, pulse rate rose significantly (p<0.05) in Normal saline (control) group following extubation. Guler G et al, in their study, showed increased heart rate during extubation in both dexmedetomidine and saline groups, but they explained that atropine used with neostigmine for reversal of the neuromuscular blockade must have contributed to the increase in heart rate at the time of extubation. [15]

In our study, we observed that in patients in the control group (Group 2), the blood pressure values (systolic, diastolic and mean BP) significantly increased from baseline immediately following reversal (T6) as well as after extubation (T7). But in Group 1, there was no rise in blood pressure; instead the BP fell below the baseline following

start of dexmedetomidine infusion (T3, T4, T5) and it remained near baseline thereafter at all points of time following extubation (Graph 2,3,4). Similar trends were noted by Jain D et al in their study, where the blood pressure did not change significantly throughout the study period in the patient group receiving dexmedetomidine in a dose of 1µg/kg; on the other hand, significant rise in systolic blood pressure was noted (*p*<0.05) following extubation in the control group.[14] In the study by Guler G et al, diastolic blood pressure increased significantly in both dexmedetomidine and control groups during extubation, but it was significantly lower in dexmedetomidine group than in control group at all times starting from 5 min after the drug administration.[15]

In our study, attempts were made to compare the extubation parameters between the two groups. We found that the time to extubation, clinically, was significantly longer, in the dexmeditomidine group as compared to the control group and this was observed to be statistically significant with *p value* <0.0001. (Table 2)

The study by Guler G & Akin A et al, in children undergoing adenotonsillectomy, noted that the children receiving dexmeditomidine demonstrated a significant prolongation of the time to extubation and emergence in comparison to the control group (*p* <0.05).[16] This is comparable to our observation in the present study.

We found a higher incidence of coughing in control group when compared to dexmeditomidine group. This matches with the findings of study done by Aksu R et al.[17] Our findings are also corroborated by Guler G & Akin A et al who found that dexmedetomidine allowed better tolerance of endotracheal tube and caused significant reduction in coughing during extubation without affecting the time to emergence, an effect possibly mediated via its sedative and analgesic effect.[16]

In our study, sedation following extubation, was assessed using Ramsay Sedation Scale (Table 3). Patients who received dexmeditomidine were found to be calm, peaceful and responded to verbal commands (score of 2) following extubation, whereas patients in Normal saline group were co-operative, oriented and restless (score of 1). This observation is in agreement with the studies done by Jain D et al[14] and Aksu R et al,[17] who did not notice sedation.

Conclusion

We conclude that a single, 0.5µg/kg body weight bolus of dexmedetomidine, when administered as an infusion, before tracheal extubation effectively helps to attenuate the airway reflexes and hemodynamic responses that occur during emergence from anaesthesia, thus rendering smooth extubation. It provides adequate sedation while maintaining patient's arousability and also delays the need for analgesia in the post-operative period.

Recommendation

Use of dexmedetomidine is highly recommended in patients undergoing general anesthesia, before extubation for smoother emergence. However, further studies are needed in a larger population, before its recommendation in patients of coronary artery disease, hypertension, cerebral vascular diseases, and neurosurgeries.

Acknowledgements

Conflict of Interest: None.

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