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Effect of Clonidine and Dexmedetomidine on Haemodynamic and Recovery Responses During Tracheal Extubation: A Randomised Double-Blind Comparative Study

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Abstract

Background and Aims: Emergence from anaesthesia and tracheal extubation are associated with transient surge in catecholamines due to sympathetic stimulation causing hypertension, tachycardia, myocardial ischaemia etc. Various drugs are being studied to attenuate the haemodynamic response to tracheal extubation. This study aimed to compare the effect of a bolus dose of different drugs of alpha 2 adrenergic agonists (clonidine and dexmedetomidine) on haemodynamic, airway reflexes and recovery responses during tracheal extubation. *Materials and methods:* ninety patients aged 20 to 45 Y of either sex of ASA gr I/II scheduled for elective surgical and gynaecological surgeries studied after randomisation into three groups. Technique of anaesthesia was standardised for all three groups. just 5 minutes before anticipated end of surgery Group A, Cand D received inj. Placebo (normal saline), Clonidine 0.75 µg/kg and Dexmedetomidine 0.5 µg/kg respectively intravenously over 2 min. Monitoring of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) were recorded at the time of bolus drug injection and there after 1,2 and 3 min after injection, during extubation, at 1, 3, 5, 10 and 15 min after extubation. Quality of extubation was evaluated immediately after extubation based on cough using five point rating score, postoperative sedation was evaluated on a six point scale. Side effects like laryngospasm, bronchospasm respiratory depression, desaturation, vomiting, hypotension, bradycardia and undue sedation were noted. *Results:* Haemodynamic parameters (HR, SBP, DBP and MAP) were significantly lower in study groups from 3 min of drug injection till the study period as compared to the placebo group. In majority of the cases the extubation quality score was 1 and 2 in study groups and score 3 in placebo group. Sedation scale was 2 and 3 group C and group D where as 2 in placebo group. *Conclusion:* Our study observes that alpha 2 adrenergic agonist are good and safe adjuvants to attenuate the stress response to emergence from anaesthesia and tracheal extubation. Dexmedetomidine behaved slightly better than clonidine to supress the haemodynamic response.

Keywords: Airway reflexes; Clonidine; Dexmedetomidine; Extubation; Haemodynamic responses.

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Introduction

Tracheal extubation is an important event in the course of general anaesthesia, which causes modest (10% to 30%) and transient (lasting 5 to 15 minutes) increase in heart rate and blood pressure [1]. Extubation is associated with reflex sympathetic discharge caused by epipharyngeal

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and laryngopharyngeal stimulation. These changes are transient and probably of no consequences in healthy individual going for surgery but has a major concern for patients with CAD, cerebrovascular disease and in hypertensive patients [2-4]. Different drugs and techniques has been used to attenuate the pressor response such as narcotic analgesics, local anaesthetics, calcium channel blockers and adrenoceptor blockers but none has been found completely successful [5,6].

Clonidine and dexmedetomidine are highly selective alpha-2 adrenergic receptor agonists without effect on respiration. They inhibit the release of catecholamines and vasopressin and thus helps to modulate the haemodynamic changes andalso has analgesic, sedative and anaesthetic sparing properties.

The present study was aimed to evaluate and compare the efficacy of clonidine and dexmedetomidine as compared to placebo on haemodynamic, airway reflexes and recovery responses during tracheal extubation.

Materials and Methods

This study was carried out from June 2016 to May 2018 after obtaining approval from the hospital ethics committee. Ninety patients of either sex (30 in each group) between 20 to 45 yr. of age belonging to ASA physical status I/II scheduled for elective general surgical and gynaecological cases under general anaesthesia. Patients suffering from cardiovascular, respiratory disorders, diabetes, hypertension, obesity, difficult airway, history of sleep apnoea, pregnancy, breast feeding women and medications that affect heart rate or blood pressure and emergency procedures were excluded from the study.

Preanesthetic check-up was conducted and a detailed history and a complete physical examination recorded. Routine investigations like complete blood picture, blood grouping and typing, blood urea, serum creatinine, bleeding time, clotting time, blood sugar, ECG and chest radiography were done. Written informed consent was taken from each patient.

Randomisation procedure

The patients were randomly divided into three groups of thirty each using computer generated sequential number placed in sealed envelopes and opened only before the commencement of the study. The study was double blinded so that the patients and the assessor were unaware of the group. Only the attending consultant administering the drugs knew the group allocation.

Group A: Placebo group

Group C: Clonidine group

Group D: Dexmedetomidine group

Anaesthesia technique was standardized for all the three groups with glycopyrrolate, midazolam, propofol, fentanyl, vecuronium, nitrous oxide-oxygen, isoflurane and IPPV with closed circuit. Standard monitoring consisted of ECG, pulse oximetry (SpO_2), $EtCO_2$ and non-invasive blood pressure. Inhalational agent was cut-off 5 minutes before the estimated time of end of surgery and patients in each group received the specified solution intravenously over 2 minutes. Patients in group A received 10 ml of normal saline, group C received clonidine 0.75 µg/kg IV in 10 mL saline and group D received dexmedetomidine 0.5 µg/kg IV in 10 mL saline over 1-2 minutes.

Heart rate, systolic, diastolic and mean arterial blood pressures were recorded at the time of bolus drug injection and there after 1,2 and 3 min after injection, during extubation, at 1, 3, 5, 10 and 15 min after extubation. Residual neuromuscular blockade was reversed with neostigmine and glycopyrrolate. When spontaneous respirations were sufficient and able to obey simple commands, suction of the throat was done, and trachea was extubated.

The anaesthesiologist performing the extubation was blinded to the study drugs. Heart rate, systolic, diastolic and mean arterial blood pressure were recorded at the time of extubation and thereafter 1, 3, 5, 10 and at 15 minutes after extubation. Any side effects like laryngospasm, bronchospasm, respiratory depression, desaturation, vomiting, hypotension, bradycardia and undue sedation were noted. Hypotension was defined as a decrease in systolic blood pressure of more than 20% decrease from baseline or systolic blood pressure less than 80 mmHg. Bradycardia was defined as heart rate of less than 60/min.

Quality of extubation was evaluated based on cough immediately after extubation, using a 5-point rating scale [7].

1. No coughing.
2. Smooth extubation with minimal coughing (1 or 2 times).
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).

Post-operative sedation was evaluated 5 minutes after extubation on a 6-point scale (Ramsay sedation scale) [8].

1-Anxious or agitated and restless or both; 2-Cooperative, oriented and tranquil; 3-Drowsy, but responds to commands; 4- Asleep, brisk response to glabellar tap or loud auditory stimulus; 5-Asleep and slow response to stimulation and 6-Asleep and unarousable, no response to stimulation.

Statistical analysis

The normality distribution of the data was confirmed by Kolmogorov-Smirnov test. The continuous data was displayed by mean and standard deviation and discrete data as Median and interquartile range (IQR).

As all the assumptions of ANOVA were accomplished. The ANOVA and ANOVA (repeated measures) was performed for haemodynamic parameters, followed by Tukey-Kramer multiple comparison analysis. The discrete data were analysed using Mann-Whitney U test. The chi-square test was performed for categorical data. The p value of < 0.05 was considered as significant.

Results

The patients in all the three groups were comparable for age, weight, male: female ratio, ASA physical status and Mallampati class. The difference between these groups were insignificant (Table 1).

Base line values of haemodynamic parameters were comparable in all the three groups. We observed statistically significant difference in HR from 3 minutes post drug administration till the study period (Table 2). When the study groups

Table 1: Demographic Variables

Variable	Group A	Group C	Group D
Mean Age±SD (Yr)	34.93±7-21	35,32±2.43	33±6.95
Male : Female	11:21	13:17	18:12
ASA Gr I/II	20/10	22/8	21/9
Mean Weight±SD(Kg)	63.43±7.95	63.94±7.14	62.43±6.84
Mean Height±SD(Cm)	154.9±6.65	156.8±12.43	155.73±8.61

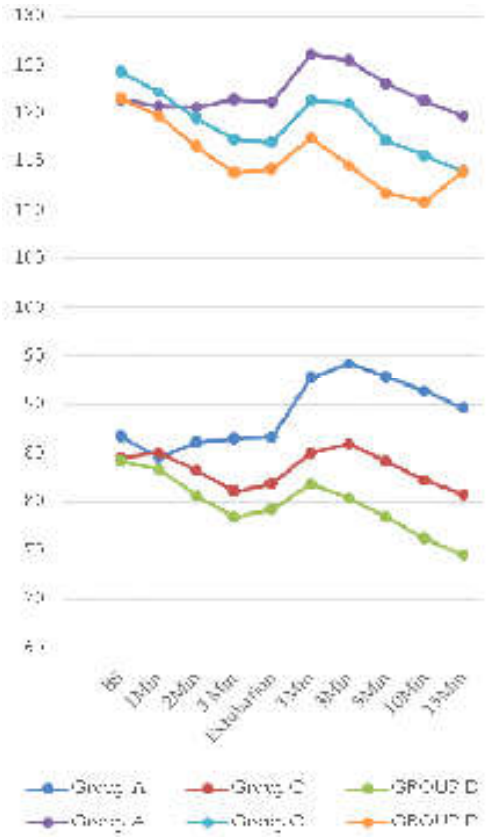

Fig 1: Changes in HR and MAP in all three groups

were compared to the placebo group significant difference was found from 2-3 minutes of drug administration till 15 min. whereas the two study groups comparison showed difference ($p<0.05$) from 3 min post extubation.

Even the SBP, DBP and MAP (table 3) showed significant difference from 3 min of drug injection till the end of the study period. Analysis between the placebo group and group C and group D was also statistically significant (Fig. 1) from 3 min onwards. The comparison between the study groups showed difference (Fig. 2) only after 1 min post extubation for SBP but no difference for DBP and MAP.

We observed statistically significant difference in the quality of extubation in the control group when compared to group C and group D. 67% of patients in the control group showed moderate coughing at the time of extubation and only 33% of the patients could be extubated smoothly with minimal coughing (Table 4). Where as in group D 60% of the patients could be extubated smoothly without any cough and 40% of the patients showed minimal coughing at the time of extubation. The Group C had smooth extubation without cough in 77% of patients and the remaining 23% with minimal cough.

Table 2: HR Variations

Heart Rate	Group A		Group C		Group D		F	P Value
	Mean	SD	Mean	SD	Mean	SD		
BS	84	8.99	84.56	7.08	84.13	9.13	0.998	0.373
1 Min	84.6	8.07	85.07	6.86	83.4	8.72	0.354	0.704
2 Min	86.07	8.23	83.27	6.96	80.67	8.49	3.487	0.035
3 Min	86.47	7.98	81	7.12	78.47	8.35	8.175	0.001
Extubation	86.6	7.6	81.8	6.98	79.2	7.67	7.675	0.001
1 Min	92.7	8.46	85.07	6.62	81.87	7.52	16.115	0.000
3 Min	94.2	7.42	86	7.52	80.4	8.15	24.378	0.000
5 Min	92.87	6.51	84.2	7.2	78.47	7.43	31.653	0.000
10 Min	91.47	6.64	82.2	7.17	76.2	7.6	34.735	0.000
15 Min	89.6	6.61	80.77	7.4	74.6	7.76	32.226	0.000

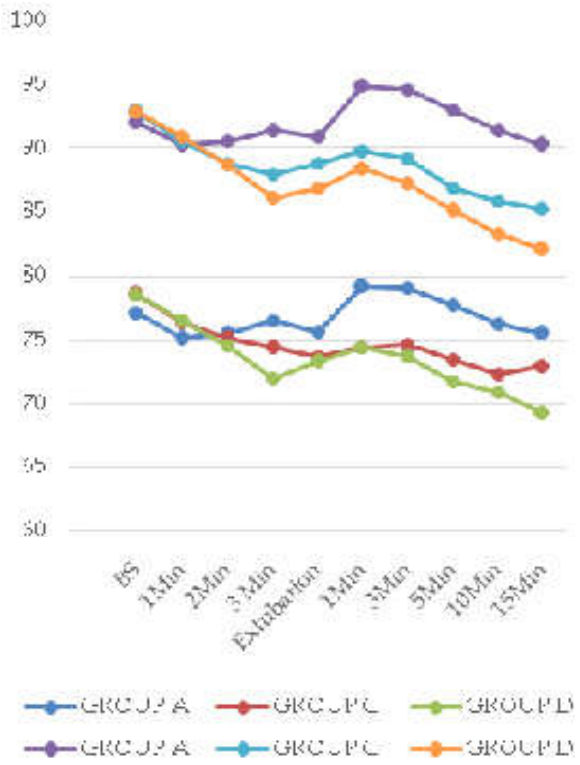

Fig 2: Changes in SBP and DBP in all three groups

Table 3: MAP Variations

MAP	Group A		Group C		Group D		F	P Value
	Mean	SD	Mean	SD	Mean	SD		
BS	91.97	3.73	92.83	4.15	92.9	4.9	4.575	0.013
1 Min	90.3	3.43	90.57	4.29	90.93	4.72	0.173	0.841
2 Min	90.53	3.48	88.83	4.35	88.7	4.39	1.845	0.164
3 Min	91.43	2.96	88	3.71	86.1	4.39	15.761	0.000
Extubation	90.93	3.23	88.87	3.58	86.9	4.12	11.573	0.000
1 Min	94.77	3.32	89.8	4.54	88.47	3.76	17.323	0.000
3 Min	94.57	2.86	89.2	4.38	87.23	3.88	30.535	0.000
5 Min	93	3.43	86.86	4.83	85.07	3.4	33.363	0.000
10 Min	91.37	3.13	85.87	4.53	83.3	2.86	35.733	0.000
15 Min	90.23	3.04	85.27	4.67	82.03	3.86	33.474	0.000

Table 4: Distribution of Extubation and Sedation Score in all threegroups

Extubation quality score				Ramsay sedation scale			
Score	Group A	Group C	Group D	Scale	Group A	Group C	Group D
1	18	0	0	1	0	0	2
2	12	30	10	2	7	14	28
3	0	0	20	3	23	16	0
4	0	0	0	4	0	0	0
5	0	0	0	5	0	0	0
				6	0	0	0

A significant difference in the level of post-operative sedation was observed between control and both the study groups ($p<0.05$) (Table 4). In group A 93% of cases were co-operative, oriented and tranquil with sedation score of 2 on Ramsay scale, 57% of patients in group C had score of 3 and the rest with score of 2 on the Ramsay sedation scale. While Dexmedetomidine group had sedation score of 3 in 77% of patients and the remaining (23%) with score of 2 on Ramsay scale.

Bradycardia was observed in one patient and hypotension in 2 patients in the Dexmedetomidine group. But none in the other two groups. The incidence of nausea and vomiting was more in group A. Other side effects like respiratory depression, laryngospasm, bronchospasm, undue sedation was not observed in any of the three groups. No significant difference in all the three groups in SpO_2 values.

Discussion

Similar totracheal intubation, extubation is also associated with haemodynamic changes due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation. The airway irritation during tracheal extubation may cause cough or difficulty in breathing and may contribute to an increase in BP [1]. These changes are transient but probably of risk concern for patients with CAD, [2] Cerebrovascular disease [3] and in hypertensive patients [4] as against negligible consequences in healthy individual going for surgery under general anaesthesia. Smooth tracheal extubation is therefore essential requiring the absence of straining, coughing, movements, breath holding or laryngospasm.

Very few studies are there in the literature where clonidine and dexmedetomidine are used for extubation to reduce the stress response. Our study aimed to evaluate and compare the effect of two different alpha-2 adrenergic receptor agonists with the placebo group. Normal saline, clonidine (0.75 µg/kg) and dexmedetomidine (0.5 µg/kg) was used in 10 ml dilution as a single bolus dose over 2 min and observed the haemodynamic response to tracheal extubation, the quality of extubation, the level of post-op sedation and incidence of complications.

Alpha-2 receptors are physiologically located presynaptic, post synaptic and extra synaptically [9] Pre synaptical receptors clinically produce more impact due to regulation of noradrenaline and ATP release through negative feedback mechanism [10]. Pharmacological studies show dexmedetomidine is 8 times more specific alpha-2 adrenoceptor than clonidine; so dexmedetomidine has more efficacy compared with clonidine [11].

The present study observed that with endotracheal extubation there was significant rise

in HR during and after extubation (from second minute onwards after drug administration, at extubation and all times post extubation) in the placebo group. Alpha-2 agonists (clonidine and dexmedetomidine) did not show significant rise in HR from the basal value. Our results are in concurrence with the Shrirang Rao et al. [12] and Anita Kholi et al. [13].

There was significant rise in the mean values of SBP, DBP and MAP values in group A at all times till post extubation as compared to base line values. Where as both group C and group D always showed stable haemodynamic till the end of study period, this is in conjunction with the study done by Bindu et al. [14] and Manisha Kapdi et al. [15]. Similarly, Kumar S et al. [11] also observed stable MAP with dexmedetomidine and clonidine during extubation.

The incidence of bradycardia and hypotension was observed in group D but not in other two groups. Bradycardia was observed in one (3.3%) patient and hypotension in two (7%) patients, but none of them required treatment. These results are like the results of Anita Kholi et al. [13] and Guler et al. [16].

Anita Kholi et al. [13] in their study concluded that dexmedetomidine caused better attenuation of pressor response, airway reflexes during emergence from anaesthesia and better sedation than clonidine. This co-relates with our study results.

Alpha-2 adrenergic receptor agonists (clonidine and dexmedetomidine) by their analgesic and sedative properties blunt airway response and thereby prevents bronchoconstriction. We observed a smooth extubation without any cough in study groups (group C and group D) while moderate cough was seen in Group A. These results are in accordance with the study of Sharma VB et al [17] and Guler et al.[16] who used dexmedetomidine in their study. Similarly, the results of Manisha Kapdi et al. [15] and Aksu R et al. [18] supports our results for study groups.

There was a significant difference in the level of postoperative sedation observed between group A and study groups (group C and group D). We observed significant number of patients had sedation score of 3 in group C and group D, while in group A most of the patients had sedation score of 2 and few had sedation score of 1. Central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus coeruleus in the brainstem plays an important role in the sedation and anxiolysis produced by dexmedetomidine and clonidine. Our findings are in conjunction with the other studies [13,14,18].

The incidence of nausea and vomiting was observed in group A. Other side effects like respiratory depression, laryngospasm, bronchospasm, undue sedation was noted in any of the three groups. SpO_2 values were comparable in all three groups with insignificant difference in our study. These observations are consistent with the study of Anita Kholi et al. [13] and Guler et al. [16].

Conclusion

A single bolus dose of clonidine or dexmedetomidine given 5 minutes before extubation attenuates the haemodynamic and airway reflexes during emergence from anaesthesia. Smooth tracheal extubation and adequate sedation with negligible side effects were also observed in this study. However, dexmedetomidine causes better attenuation of haemodynamic and airway reflexes with undue sedation than clonidine.

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Conflict Of Interest: Nil

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