Esmolol and Dexmedetomidine to Attenuate Cardiovascular responses to tracheal extubation in patient undergoing elective surgeries under general anaesthesia: A comparative double-blind randomized trial

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***Abstract*- Background: Tracheal extubation in patients under general anaesthesia is done at the end of the surgery. Extubation is often accompanied by unpredictable and variable hemodynamic changes and respiratory tract complications. Dexmedetomidine, a selective α2 adreno receptor agonist, and Esmolol a selective beta 1 blocker is compared in this study to know which will more effective in reducing the stress of extubation in patients undergoing general anaesthesia.**
Material and methods: This study was a double-blind randomized trial conducted in department of anaesthesia and critical care, Tezpur medical college and hospital, Tezpur. A total of 70(seventy) patient were selected and divided into two groups A and B 35 each. Group A patients received intravenous Esmolol hydrochloride 1.5 mg/kg diluted with 0.9% normal saline to 10 ml and Group B patients received intravenous Dexmedetomidine Hcl 0.5 µg/kg diluted with 0.9% normal saline to 10 ml over 15 minutes before anticipated time of end of surgery. Anaesthesia technique were standardized. Heart rate, systolic, diastolic, mean arterial blood pressure were recorded and was compared among proposed groups.
Results: In this study it was found that hemodynamic changes during extubation was better tolerated by group B patients than group A patients.
Conclusion: From this study it was concluded that Dexmetomedine facilitates smoother extubation than Esmolol in patient undergoing surgery under general anaesthesia.

***Keywords*: α2 adrenoreceptor agonist, Dexmedetomidine, extubation, hemodynamic**

INTRODUCTION:

Tracheal extubation is a critical step in the process of general anesthesia. Extubation irritates the airways, resulting in coughing or straining, all of which are known to raise systolic, diastolic, and arterial pulse pressure. Coughing can raise intrathoracic pressure, interfering with a venous return to the heart. Reflex sympathetic discharge induced by epipharyngeal and laryngopharyngeal stimulation causes a considerable rise in heart rate and arterial pressure, which may last throughout the recovery phase[1].
Although the frequency of extubation failure or reintubation following surgery in the operating room (OT) is very low (0.1–0.45%), it leads to an increase in overall mortality[2]. In guidelines, many airway societies have raised concerns[3].Concerns with extubation have been prominently highlighted in the American Society of Anesthesiologists Closed Claims Analysis and National Audit Project . (NAP4)[4,5] The NAP4 study investigated airway-related difficulties and discovered a 5% mortality risk in patients with extubation failure following general anesthesia.
Deep anesthesia extubation reduces hemodynamic and respiratory reactions such as hypertension, tachycardia, dysrhythmias, coughing, laryngospasm, myocardial ischemia, and elevated intracranial and intraocular pressures[6].It may, however, be associated with an increased risk of upper airway blockage and aspiration. To avoid such complications, the All-India Difficult Airway Association (AIDAA) suggests employing a supraglottic airway device (SAD) as a bridging device. In the circumstances with a full stomach, this procedure should be avoided (obese, pregnant, recent ingestion of food, or raised intra-abdominal pressure)[7]. Exchange with SAD avoids any reflex response due to tracheal tube intolerance or its removal at emergence from anesthesia[8,9]
Esmolol is a beta-adrenergic receptor antagonist with a short half-life that is rapidly degraded by plasma esterase[10]. It is more effective than fentanyl, alfentanil, nitroglycerine, diltiazem, and lidocaine for providing hemodynamic stability during laryngoscopy, tracheal intubation, and extubation. Esmolol's quick onset and brief duration of action (T1/2 = 9 min) make it an appropriate drug for preventing the initial increases in heart rate and arterial pressure that occur after extubation[10].
Dexmedetomidine is a highly selective alpha (α)2adrenergic receptor agonist and an imidazole derivative. α2agonist causes noradrenergic neuron hyperpolarization and inhibition of neuronal activity in the locus coeruleus, resulting in reduced systemic noradrenalin release and attenuation of sympathoadrenal responses and hemodynamic stability during laryngoscopy and tracheal intubation[11].Premedication as part of a multimodal anaesthetic regimen, avoidance of emerging delirium, and pain relief in the postoperative phase are all perioperative uses of dexmedetomidine[12].Dexmedetomidine premedication not only provides anxiolysis, drowsiness, and analgesia, but it also helps to reduce the stress reactions to tracheal intubation/extubation and awakening from anesthesia. When delivered via non invasive buccal or nasal route, dexmedetomidine has a high bioavailability [13].

Material and Methods
Study design
Prospective double blind randomised study
Study site
Department of Anesthesia and Critical care, Tezpur Medical college and Hospital,Tezpur,Assam which is a tertiary care hospital.
Study duration
June 2021 to May 2022
Ethical clearance: Clearance was taken from the Institutional Ethics Committee of TMCH prior to the commencement of the study.

Sample size
Assuming the level of significance (α) 5% and the power of the study 80%, the sample size for our study has been calculated using formula of stastiscal power analysis. Wishing to detect a difference of 15 mm hg in the duration of analgesia and considering a standard deviation of 27 from a previous study, we found that 27subjects per group would be needed to answer our research question. Considering the 10% chance of loss of follow-up, we will include 35 patients in each group by rounding off for our study population.

Inclusion Criteria
Patients having age group between 18 and 45 yrs of both sexes, belonging to ASA (grade I and II) being admitted in General Surgery ward of Tezpur Medical College and Hospital and scheduled for elective general surgical procedure under general anaesthesia.

Exclusion criteria
- Patient's refusal to participate.
- Patients having known allergy to either of study drugs.
- Patients requiring emergency surgery.
- Patients having remarkable history of cardio vascular, metabolic or psychological disorder.
- Patients having difficult airway.
- Patients on medications that effect heart rate or blood pressure.
- Pregnant/lactating women

Consent
Study was done after getting written and informed consent from study groups
Randomization
Patients in Group A: Will receive esmolol in bolus dose of 1.5 mg/kg (mixed in 10ml NS)intravenously (iv) 2mins prior to tracheal extubation
Patients in Group B: Will receive dexmedetomidine 0.5 mcg/kg(mixed in 10ml NS) intravenously 2 minutes prior to extubation. Heart Rate(HR), Mean Arterial Pressure(MAP), Systolic Blood Pressure (SBP),Diastolic Blood Pressure(DBP) will be recorded at the start of study drug injection(at 0min) and thereafter at 1, 3, 5, 10 and 15 minutes after extubation. Residual neuromuscular blockade will be reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01mg/kg. Suction of throat and extubation will be carried out once the patient's spontaneous respiration is sufficient and patient become able to obey simple commands. Occurance of any events like bronchospasm, laryngospasm coughing, desaturation, respiratory depression, vomiting, bradycardia or any undue sedation will be noted.

Technique
70 patients were randomly divided into two equal groups (of 35each) after taking informed consent. In operation theatre , five lead electrogram, HR,pulse oxymetry and non invasive blood pressure were recorded. Intravenous line was secured through a 18 gauze cannula. General anaesthesia was induced with glycopyrrolate 0.2mg,fentanyl 2mcg/kg, followed by propofol 2mg/kg IV .Tracheal intubation was facilitated with atracurium besylate 0.5mg/kg IV. All patients were mechanically ventilated at fresh gas flow 4L/min to maintain an end tidal carbon dioxide(etco2) of 35-45 mm Hg .Anaesthesia was maintained with sevoflurane 0.8-1 minimum alveolar concentration (MAC) with nitrous oxide and oxygen(60:40) and atracurium besylate 0.1mg/kg iv. Inhalational anaesthetic was turned off at the end of surgery. A computer generated randomization chart was used to assign each patient in the study group.

Statistical methods
Descriptive analysis was carried out for frequency and proportion for categorical variables. Non-normally distributed quantitative variables were summarized by the median and interquartile range (IQR). Data was also represented using appropriate diagrams like pie diagrams, Error bar charts, Cluster bar charts & Line charts
All Quantitative variables were checked for normal distribution within each category of an explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro- Wilk test was also conducted to assess normal distribution. Shapiro will test p-value of >0.05 was considered as a normal distribution.
For normally distributed Quantitative parameters, the mean values were compared between study groups using an Independent sample t-test (2 groups). Categorical outcomes were compared between study groups using the Chi-square test.P value <0.05 was considered statistically significant. Data were analyzed by using coGuide software [14]

Results and observation

In table 1 the mean Age (in years)of Group Awas 36.97 ± 7.60 and Group Bwas 35.31 ± 8.46, and the mean difference (1.66) between two Groups was statistically not significant (P value 0.3917).

In table 2 Group A, 24 (68.57%) participants were ASA 1 and 11 (31.43%) were ASA 2. In Group B, 29 (82.86%) participants were ASA 1 and 6 6 (17.14%) were ASA 2. The difference in the proportion of ASA between the Study Groups were statistically not significant (P value 0.1634)

In table 3 Group A, 12 (34.29%) were male and 23 (65.71%) were female. In Group B, 11 (31.43%) were male and 24 (68.57%) were female. The difference in the proportion of gender between the Study Group was statistically not significant (P-value 0.7991).

In table 4 the mean Weight (in kg)of Group A was 56.17 ± 5.34 and Group B was 57.17 ± 4.45, and the mean difference (1.01) between two Groups were statistically not significant (P value 0.3976).

Table 1&2: Age (kg) and ASA distribution in the Study Group

Parameter	Study Group		P value (IST)
	Group A (N=35)	Group B (N=35)	
Age (in years)	36.97 ± 7.60	35.31 ± 8.46	0.3917

ASA Risk	Study Group		P value
	Group A (N=35)	Group B (N=35)	
ASA 1	24(68.57%)	29 (82.86%	0.1634
ASA 2	11 (31.43%)	6 (17.14%	

Table 3 &4: Gender distribution and weight distribution

Gender	Study Group		P value
	Group A (N=35)	Group B (N=35)	
Male	12 (34.29%)	11 (31.43%)	0.7991
Female	23 (65.71%)	24 (68.57%)	

Parameter	Study Group (Mean ± SD)		P Value
	Group A (N=35)	Group B (N=35)	
Weight (in kg)	56.17 ± 5.34	57.17 ± 4.45	0.3976

In figure 1 The mean difference in Systolic BP (mm of hg) at different time periods like preoperative , intra operative and before extubation between the two Study Group (Group A & Group B) was statistically not significant whereas significant difference was found in Systolic bp at different time periods like at 1min, at 3 min,at 5 min, 10 min and 15 min. The mean of Systolic bp at 1,3,5,10 and 15 minutes was high in Group A compared to Group B whereas Systolic bp at pre-operative was high in Group B compared to Group A

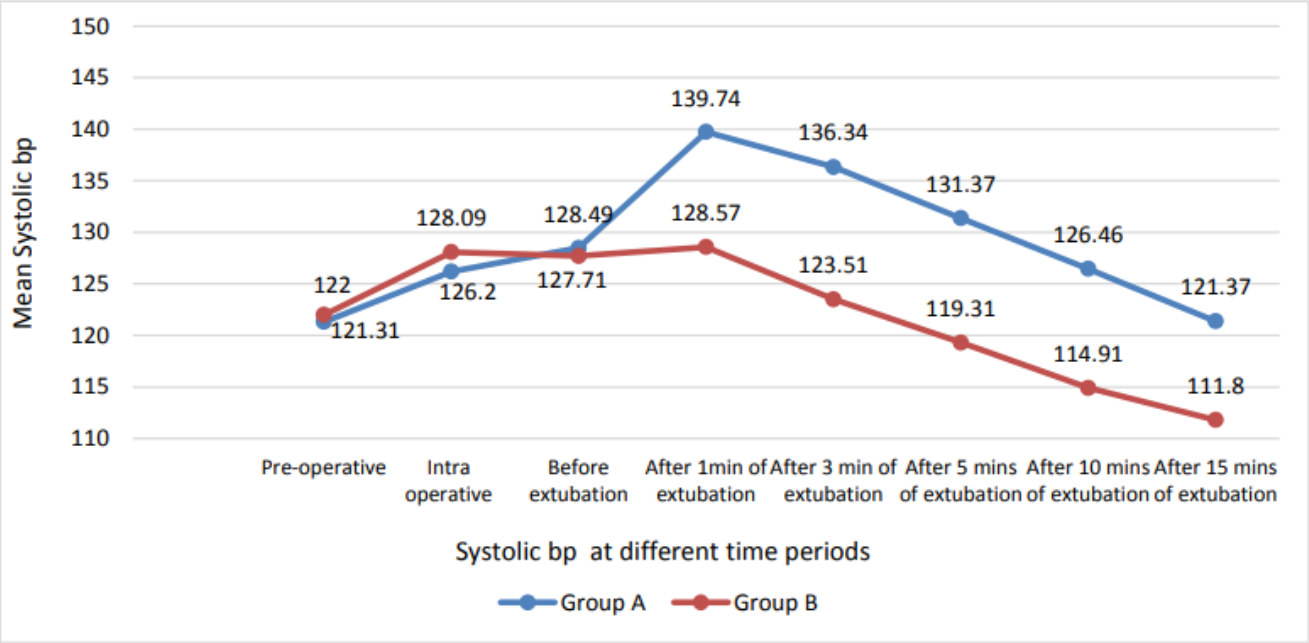

Figure 1: Line chart of Comparison of Systolic BP (mm of hg)

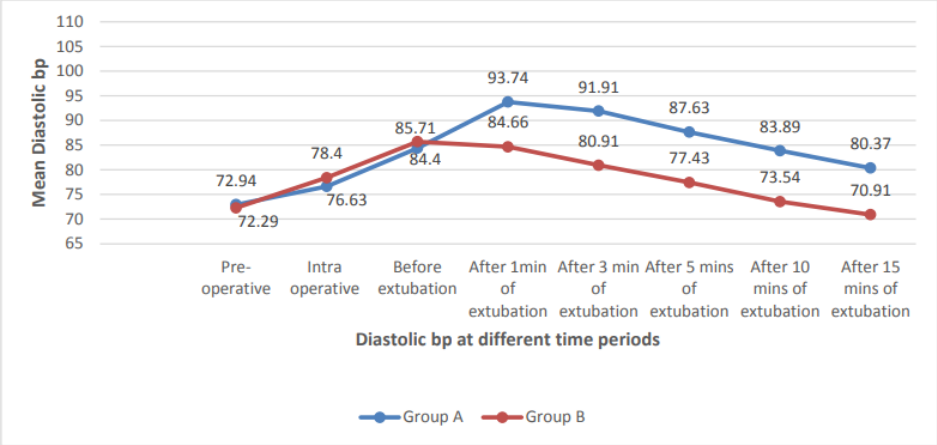

Figure 2 : Line chart of comparison of diastolic BP (mm of Hg)

The mean difference in Diastolic BP (mm of hg) at different time periods like preoperative, intra operative & before extubation between the two Study Group (Group A & Group B) was statistically not significant (P value >0.05), whereas significant difference was found in Diastolic bp at different time periods like after extubation at 1min, at 3 min,at 5 min, at 10 min & at 15 min. The mean of diastolic bp at 1,3,5,10,15 minutes is high in Group A Compared to Group B whereas Diastolic bp at Intra operative was high in Group B compared to Group A (figure 3).

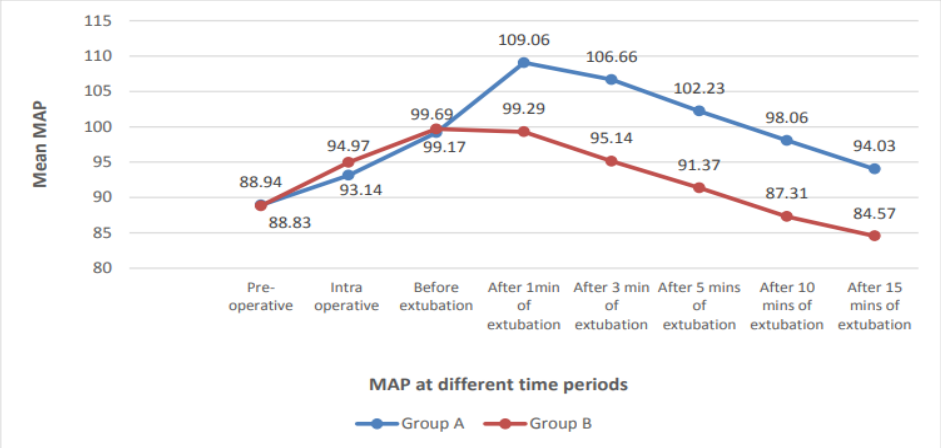

Figure 3:: Line chart of Comparison of MAP with the Study Group

The mean difference in MAP at different time periods like Pre-operative, Intra operative &Before extubation between the two Study Group (Group A & Group B) was statistically not significant (p value >0.05), whereas significant difference was found in MAP at different time periods like after extubation at 1min, at 3 min,at 5 min, at 10 min& at 15 min. The mean of MAP after extubation at 1 min is little high in Group A Compared to Group B whereas MAP at Intra operative was high in Group B compared to Group A(figure 4)

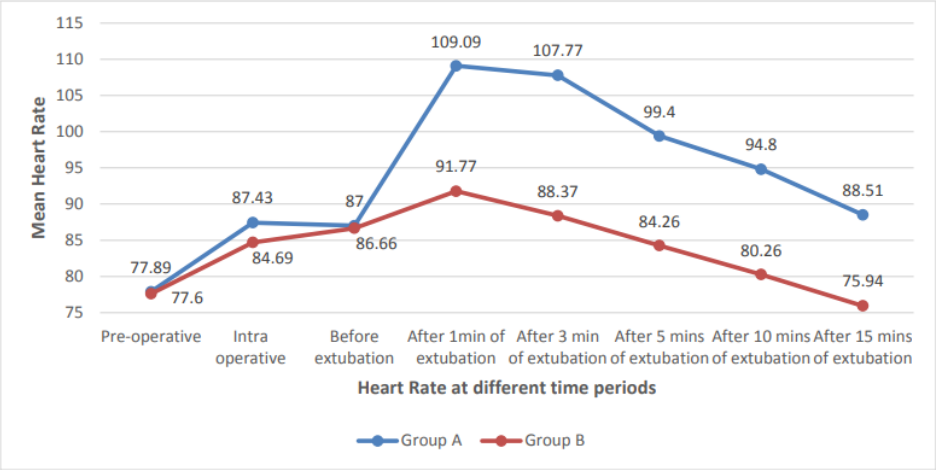

Figure 4: Line chart of Comparison of Heart Rate with Study Group (N=70)

The mean difference in Heart Rate at different time periods like Pre-operative, Intra operative&Before extubation between the two Study Groups (Group A & Group B) were statistically not significant (P value >0.05), whereas significant difference was found in Heart Rate at different time periods likeafter extubation at 1min, at 3 min,at 5 min, at 10 min& at 15 min. The mean of Heart Rate at all time points little high in Group A Compared to Group B.(figure 5).

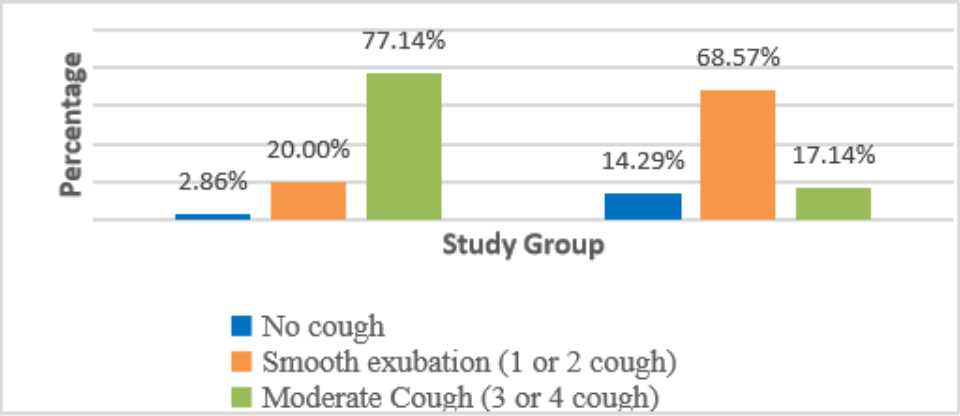

Figure 5: Cluster Bar chart of Comparison of Quality of extubation Score

In Group A, in Quality of extubation Scores, 7 (20.00%) participants were Smooth exubation (1 or 2 cough)&27 (77.14%) were Moderate Cough (3 or 4 cough). In Group B, 24 (68.57%) participants were Smooth exubation (1 or 2 cough)&6 (17.14%) were Moderate Cough (3 or 4 cough). The difference between the proportion of Quality of extubation Scores between the study group was statistically significant (P-value <0.001).

DISCUSSION

Extubation causes restlessness, pain, anxiety, and airway irritation, which can result in haemodynamic responses similar to intubation, such as hypertension, tachycardia, and arrhythmias. It is more dangerous in patients who have hypertension, myocardial insufficiency, or cerebral vascular disease, and is linked to an increased risk of cerebral haemorrhage, myocardial ischemia, and pulmonary oedema.

The current study was a randomised controlled trial to compare the efficacy of intravenous Esmolol 1.5 mg/kg bolus and Dexmedetomidine 0.5 µg/kg on hemodynmamic response during tracheal extubation in elective surgical procedures.

Esmolol is a short-acting selective beta-blocker, and beta-adrenergic blockers are commonly used to suppress adrenergic activity caused by extubation. Because esmolol has a very short half-life, IV bolus dose of esmolol was used in this study. Dexmedetomidine has been used successfully to reduce the hemodynamic effects of tracheal intubation. The current study was conducted to evaluate the effect of dexmedetomidine in a dose of 0.5 µg/kg on hemodynamic responses during extubation, the quality of extubation, the level of postoperative sedation, and the prevalence of complications, based on its characteristics of sedation, hemodynamic stability and lack of respiratory depression, as well as its analgesic effects[15]

In the present study we used esmolol 1.5mg/kg body weight diluted in 10ml 0.9% normal saline before induction and compared with dexmedetomidine 0.5 mcg/kg body weight diluted in 10ml 0.9% normal saline before induction. Following are some studies where both the drugs have been used in different doses for attenuating the adverse hemodynamic stress response to extubation.

The heart rate was lower in the Dexmedetomidine group at all times post extubation. The difference was statistically significant till 15 minutes post exubation. The p values were less than 0.001 at 1, 3, 5, 10 and 15 minutes post extubation.
Bindu et al [15](2013) used 0.75 mcg/kg dexmedetomidine in a placebo controlled randomized double-blind study to evaluate its effects on hemodynamic response associated with extubation.
In another similar study by Tendulkar, M et al compared the hemodynamic parameters of Esmolol and Dexmedetomidine in extubation, they found that despite the fact that Injection Esmolol successfully controlled the hemodynamic response to extubation, the attenuation was more pronounced with Injection Dexmedetomidine, as the parameters were below baseline values at all times after extubation, with no excessive bradycardia or hypotension.. They also found Group Dexmedetomidine had a higher quality of extubation than Esmolol
In this study we found that the mean Systolic BP was low in Dexmedetomidine Group at all times post extubation compared to Esmolol Group.
The mean of MAP after extubation at all time after extubation was high in Group A Compared to Group B whereas MAP during Intra operative period was high in Group B compared to Group A. Sharma, V et al109 study found in there study that dexmedetomidine group, with increased MAP during the first three minutes of drug administration. However, dexmedetomidine reduced the increase in blood pressure more than lignocaine. Activation of alpha 2 receptors in the central nervous system causes a decrease in sympathetic outflow and an increase in vagal activity. Dexmedetomidine may act as a peripheral ganglionic blocker, which may enhance the sympatholytic effect. Turan et al.[16] investigated the effects of administering dexmedetomidine at the end of the procedure to prevent hyperdynamic responses during extubation and to allow for a comfortable and high-quality recovery. They discovered that dexmedetomidine 0.5 µg/kg given 5 minutes before the end of surgery stabilized haemodynamics, allowed for easy extubation, and allowed for a more comfortable recovery and early neurological examination after intracranial surgery.
The quality of extubation was better with Group B (dexmedetomidine) compared to Group A (esmolol group).Tendulkar, M etal[17] found group dexmedetomidine had a a higher quality of extubation than esmolol. Patients in the dexmedetomidine group were significantly more sedated than those in the esmolol and control groups, but this aided in a smooth extubation with no agitation. Similar finding was found in our study.
Central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus coeruleus in the brainstem plays a prominent role in the sedation and anxiolysis produced by dexmedetomidine. Decreased noradrenergic output from the locus coeruleus allows for increased firing of inhibitory neurons including the g-amino butyric acid system resulting in anxiolysis and sedation. We found that in Group A, in Ramsay sedation score @15 minutes, majority 80% were cooperative, oriented and tranquil, 11.43%were drowsy but responds to commands and only 8.57% were anxious or agitated or both. In group B nearly half of the subjects (51.43%) were drowsy but responds to commands and 48.57% were Cooperative, oriented and tranquil. The difference between the proportion of Ramsay sedation Score @15 minutes between the study group was statistically significant.
This finding is supported by Konda S et al[18] where they compared esmolol and propofol and found esmolol group with no sedation at 10 min but after 10 mins both were comparable. In another study by Shrirang Rao M et al113, following extubation, a significant number of patients in the dexmedetomidine group (46%) were drowsy but responded to oral commands (score of 3) as opposed to 80% of patients in the control group who were cooperative and oriented (score of 2). This observation was consistent with Basar et al[19] comparative study of dexmedetomidine and fentanyl in rhinoplasty patients[19] However, in contrast to Jain et al[20],who did not notice sedation in either group..

Limitations and recommendations

- A dose response study could help determine the best dose of the study drugs.
- Peripheral Nerve Stimulator was not used to assess reversal of the subjects.
- The small sample size is another limitation.
- However, in order to have more than 80% power, we needed a sample size of about 80 patients in each group, which was logistically challenging for us.

CONCLUSION

From this present study, it can be concluded that both Esmolol and Dexmedetomidine both attenuate haemodynamic responses during tracheal extubation. However, the quality of extubation was better in Dexmedetomidine group compared to Esmolol group but patients were more sedated in Dexmedetomidine group
Conflict of interest: None declared
Source of funding: Non

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