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Comparing different doses of dexmedetomidine in attenuating extubation response in chronic smokers undergoing total extraperitoneal laparoscopic inguinal hernia repair: a randomized prospective study

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Abstract

Background: During the process of emergence from general anesthesia, tracheal extubation is a very critical step. Tracheal extubation is not just a reversal of intubation, as during extubation we encounter a change of state from controlled conditions to an uncontrolled environment. We have aimed our study at evaluating the attenuating effect on the extubation response using three different doses of dexmedetomidine on patients who are smokers and undergoing total extraperitoneal laparoscopic inguinal hernia repair under general anesthesia. This randomized, controlled, triple-blinded study included 90 smokers aged between 40 and 60 years. These patients were randomized to receive dexmedetomidine 0.5 μg/kg (group A), 0.75 μg/kg (group B), and 1 μg/kg (group C) prepared as a 10 ml infusion started 10 min before patients were extubated. Extubation quality, hemodynamic changes, oxygen saturation, sedation, and postoperative complications were evaluated.

Results: The extubation quality became better, sedation and incidence of bradycardia in the post-operative period increased with a higher dose of dexmedetomidine. Attenuation of hemodynamic parameters was observed after 4 min of starting infusion and during extubation in each group and was found to be significant ($P < 0.001$).

Conclusions: It was concluded that dexmedetomidine when used at a dose of 0.75 μg/kg provided excellent extubation conditions with stable hemodynamic parameters in chronic smokers with minimal sedation and no other adverse effects.

Keywords: Airway extubation, Dexmedetomidine, Hemodynamic, Smokers, Sedation

Background

Smokers, because of their exaggerated upper airway reflexes, have an increased risk of developing complications during extubation which may lead to laryngospasm, hypoventilation, hypoxemia, and reintubation. Tracheal extubation is often accompanied by a rise in plasma catecholamines leading to undesirable events which include, hypertension, and tachycardia (Hartley and Vaughan 1993; Derbyshire et al. 1983).

Many complications such as cardiac arrhythmias, myocardial ischemia, cerebrovascular hemorrhage, pulmonary edema, and cardiac failure have also been reported at the time of extubation. Hence, it becomes necessary

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to control all adverse factors associated with extubation. Many studies have been conducted to control hemodynamic stress response with dexmedetomidine which is selective alpha-2 (α-2) agonist (Turan et al. 2008; Manne et al. 2014; Bilgi et al. 2016; Mahajan et al. 2018), but still, there is a paucity of data when it is used, to attenuate extubation response in smokers

In our study, we compared three different doses of dexmedetomidine used as an infusion to attenuate extubation response in smokers and thereafter find the most suitable dose. We hypothesize that dexmedetomidine when used in higher recommended doses may result in the production of stable hemodynamics during extubation but could be associated with adverse effects. We aimed to observe airway response and hemodynamic changes during extubation in chronic smokers following infusion of three different doses of dexmedetomidine.

Methods

We conducted our study at a tertiary care hospital and research center from September 2019 to February 2020 after the institutional ethical committee approval (No. HFW-H-DRPGMC/Ethics/2017-58) and was registered via clinical trial registry: CTRI/2019/08/020728. This manuscript adheres to the applicable CONSORT guidelines.

The prospective randomized triple-blinded controlled trial included 90 adults, current smokers aged between 40 and 60 years that were found to have used a minimum of 100 cigarettes. They currently smoke cigarettes daily or intermittently. (Schane et al. 2010) These patients had an American Society of Anesthesiologists (ASA) physical status II and were kept for total extraperitoneal laparoscopic inguinal hernia repair under general anesthesia.

We included the following exclusion criteria such as a history of diabetes mellitus, cerebrovascular diseases, untreated hypertension, severe cardiovascular disease, renal disease, drug hypersensitivity, and patient refusal. If surgery took more than 10 min to complete after the start of infusion or if there was an episode of bradycardia ($HR < 50$ bpm) or fall in systolic blood pressure (SBP) less than 80 mm or if it rose more than 180 mm of Hg any time during the conduct of the study, patients were excluded from the study and managed accordingly.

The patients were sampled using simple stratified random sampling. Randomization into three equal groups was done by assigning the random number generated by the computer in form of a sealed envelope. The first anesthesiologist opened the envelope after taking the patient into the operating theater (OT). The code obtained was delivered to a second anesthesiologist who made the drug to be administered in a 10 ml syringe. The drug was prepared and was given to anesthesiologist (third anesthesiologist) present in the OT, who administered the drug and recorded observations.

We obtained fresh written informed consent before surgery. On the night before surgery, tablet alprazolam 0.5 mg was given, and the patients remained fasting for 8 h. After premedication, smoking was not allowed. Patients under study were divided into three groups ($n = 30$). The drug was prepared as an infusion with normal saline with a total volume of 10 ml. Group A received 0.5 μg/kg of dexmedetomidine in normal saline, group B received 0.75 μg/kg of dexmedetomidine in normal saline, and group C 1 μg/kg of dexmedetomidine in normal saline. On arrival in the operation theater, an 18G i.v. a cannula was secured, and standard monitoring such as SpO2, five lead electrocardiography, noninvasive blood pressure, and neuromuscular monitor was attached. All patients received premedication in the form of Inj. glycopyrrolate 0.2 mg i.v., Inj. ondansetron 4 mg i.v., and Inj. ranitidine 40 mg i.v. as per the institutional protocol.

After premedication, the induction of anesthesia was done with Inj. propofol 2–2.5 mg/kg and Inj. fentanyl 2 μg/kg. When there was no response to a train of four after using Inj. vecuronium 0.1 mg/kg, patients were intubated. Anesthesia maintenance was done with the use of isoflurane 0.5–1.5% with nitrous oxide (N2O) 60% in oxygen and using Inj. vecuronium as and when required. End-tidal carbon dioxide pressure (ETCO2) was kept between 30 and 35 mm Hg. Inj. diclofenac 75 mg intravenously and paracetamol 1 g infusion were given to every patient intraoperatively.

Isoflurane was discontinued at the beginning of skin closure, and dexmedetomidine infusion was started only when patients showed initial signs of respiratory effort. In group A, infusion of 0.5 μg/kg dexmedetomidine diluted to 10 ml in normal saline was started and given over 10 min using an infusion pump. In group B, 0.75 μg/kg and in group C 1 μg/kg dose of dexmedetomidine was used respectively for infusion. After dexmedetomidine was infused over 10 min, all patients were extubated within 5 min of discontinuing the infusion. Before extubation, nitrous oxide was discontinued, and muscle relaxation was reversed using neostigmine 0.05 mg/kg with glycopyrrolate 0.01 mg/kg i.v. The reversal was given when at least 2 to 4 responses to train of four were present and the trachea was extubated at a TOF ratio of > 0.9.

The primary outcome included quality of extubation assessed by 5-point scale (Bindu et al. 2013), and any adverse event like hypotension, hypertension, and bradycardia was noted. The secondary outcomes included postoperative sedation in patients after extubation. In the postanesthesia care unit, hemodynamic variables were observed at an interval of 1 min for 5 min and thereafter for 15 min up to 2 h. For sedation,

Ramsay Sedation Scale (RSS) (Sessler et al. 2008) was used at 5-min intervals for 30 min and subsequently every 30 min until 90 min.

The sample size was based on the objectives of the project, time availability, and the necessary degree of precision. Also, a reference was made following a prior published study conducted by Luthra et al. (Luthra et al. 2017) in which ninety patients (30 in each group) were calculated at 80% power and a type 1 error of 0.05. All the data was entered into a Microsoft spreadsheet and was analyzed using SPSS 17.0 software. Categorical data were compared using the chi-square test and ANOVA test with post hoc Tukey HSD tests. The *P*-value < 0.05 was considered to be significant, and the *P*-value < 0.001 was highly significant.

Results

We screened 118 current smokers out of whom 90 patients were enrolled in our study that fulfilled the eligibility criteria. After exclusion, each group was allocated 30 patients randomly, and an analysis was made (Fig. 1).

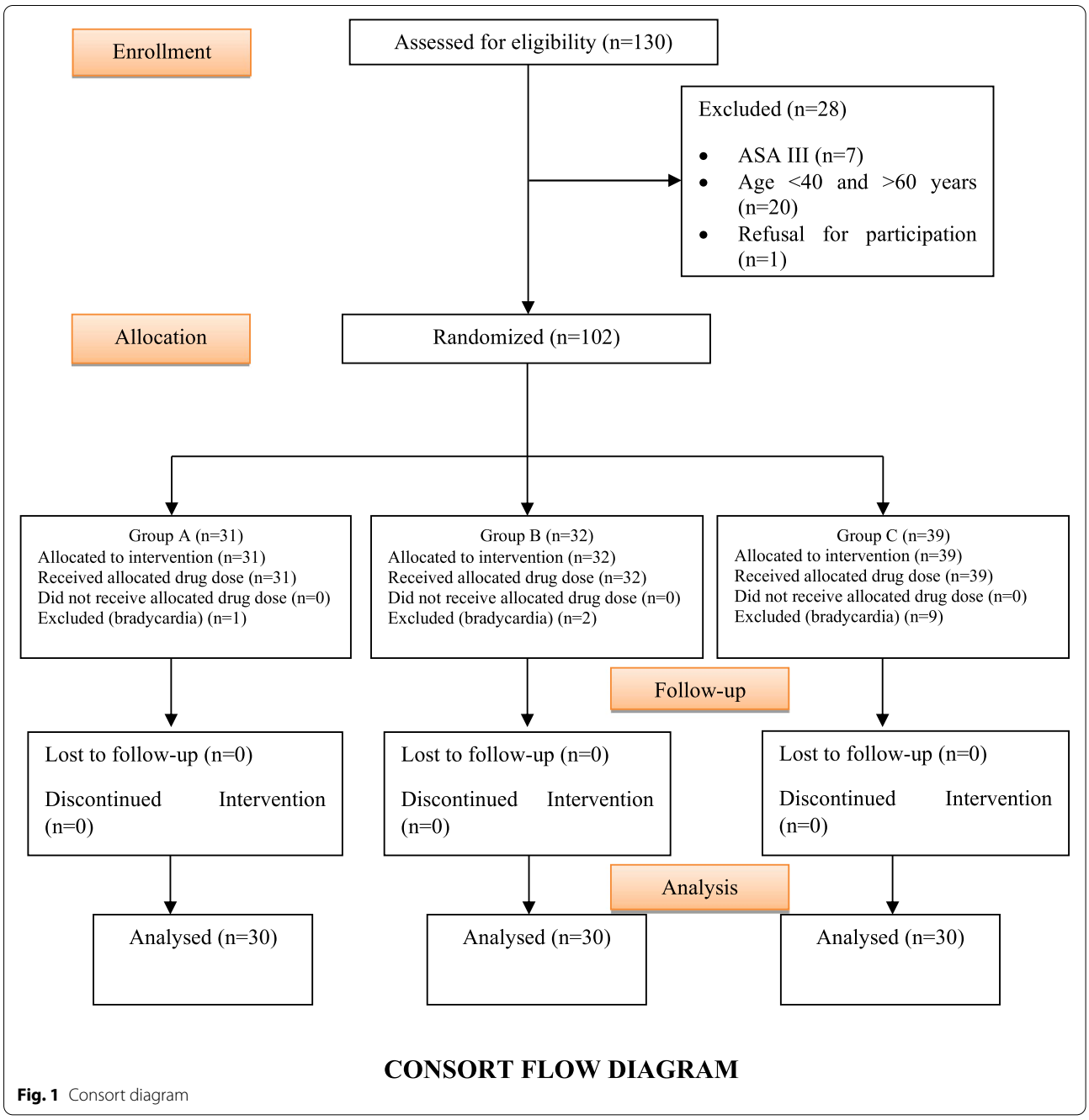

Fig. 1 Consort diagram

Three groups were found to be comparable concerning demographic profiles with a *P*-value > 0.05 (Table 1).

In comparing group A with group B and group C, the quality of extubation was found to be significantly poorer in group A ($P = 0.001$). In group C, 60% (18/30) of patients had no cough, while 10% (3/30) patients had a moderate cough, 30% (9/30) had a minimal cough, and none of the patients had a severe cough. In group B, 46.7% (14/30) patients had no cough, while 13.3% (4/30) patients had a moderate cough, 12 (40%) had a minimal cough, and none of the patients had a severe cough. In group A, 16.7% (5/30) patients had no cough, while 16 (53.3%) patients had a moderate cough, 10% (3/30) had a minimal cough, and 1 (3.3%) patient had a severe cough. The extubation quality was comparable between group B and group C ($P = 0.658$) (Table 2).

On comparing the heart rate in various groups, we found that it was comparable in all three groups at the start of dexmedetomidine infusion. However, we found that the heart rate was lower in group B and group C as compared to group A. Although when a comparison was made between group B and group C, the heart rate was lower in group C. When we compared the change in heart rate from the beginning of infusion up to the extubation, we found the results to be statistically significant. We found the comparison of group A with group B ($P = 0.003$), group B with group C ($P < 0.0001$), and group A with group C ($P < 0.0001$) to be statistically significant. The mean change in HR post-extubation (Fig. 2) was statistically significant between group A and group B ($P < 0.0001$) up to 30 min, group A and group C ($P < 0.0001$) until 2, and was not statistically significant between group B and group C ($P = 0.046$). One patient in group A, two patients in group B, and nine patients in group C showed an incidence of bradycardia which was instantly treated with Inj. atropine 20 µg/kg IV.

When we compared the SBP, DBP, and MAP between group A and group B, it was found to be statistically insignificant from the start of infusion up to 3.5 min and was

Table 1 Demography and clinical data

	Group A ($n = 30$)	Group B ($n = 30$)	Group C ($n = 30$)	*p*-Value
Age (years)	50.57 ± 6.36	48.13 ± 5.43	51.17 ± 5.75	0.111
BMI (kg/m^2)	20.27 ± 1.5	21.09 ± 1.5	21.09 ± 1.68	0.063
Sex				
Male, *n*	30	30	30	NA
Female, *n*	0	0	0	NA
Smoking index				
Mild (≤ 100)	0	0	0	
Moderate (101–300)	30	30	30	NA
Heavy (> 300)	0	0	0	
Duration of surgery (min)	61.67 ± 8.74	61.71 ± 7.47	57.68 ± 6.79	0.073

BMI Body mass index, *min* minutes, value of $p < 0.05$ is significant, *NA* Not applicable, *n* number

Table 2 Quality of extubation and hemodynamic parameter at extubation of the three groups

		Group A ($n = 30$)	Group B ($n = 30$)	Group C ($n = 30$)	*p*-Value
Quality of extubation, *n* (%)	1	5 (16.7%)	14 (46.7%)	18 (60%)	< 0.001*
	2	8 (26.67%)	12 (40%)	9 (30%)	
	3	16 (53.3%)	4 (13.3%)	3 (10%)	
	4	1 (3.3%)	0	0	
	5	0	0	0	
Heart rate (bpm), mean ± SD		87.5 ± 12.80	76.83 ± 9.05	59.77 ± 1.01	< 0.0001**
MAP (mmHg), mean ± SD		97.87 ± 3.6	84.73 ± 6.49	81.17 ± 6.6	$P_{A\text{-}B} < 0.0001$** $P_{A\text{-}C} < 0.0001$** $P_{B\text{-}C} = 0.878$**
Time of extubation (min), mean ± SD		8.60 ± 0.51	8.83 ± 0.51	9.34 ± 0.48	0.058**
SpO2 (%), mean ± SD		98.4 ± 1.2	98.4 ± 1	98.5 ± 1.1	0.963**

*Chi-square test applied for quality of extubation, **ANOVA test. *SD* standard deviation, *MAP* mean arterial pressure, SpO_2 oxygen saturation

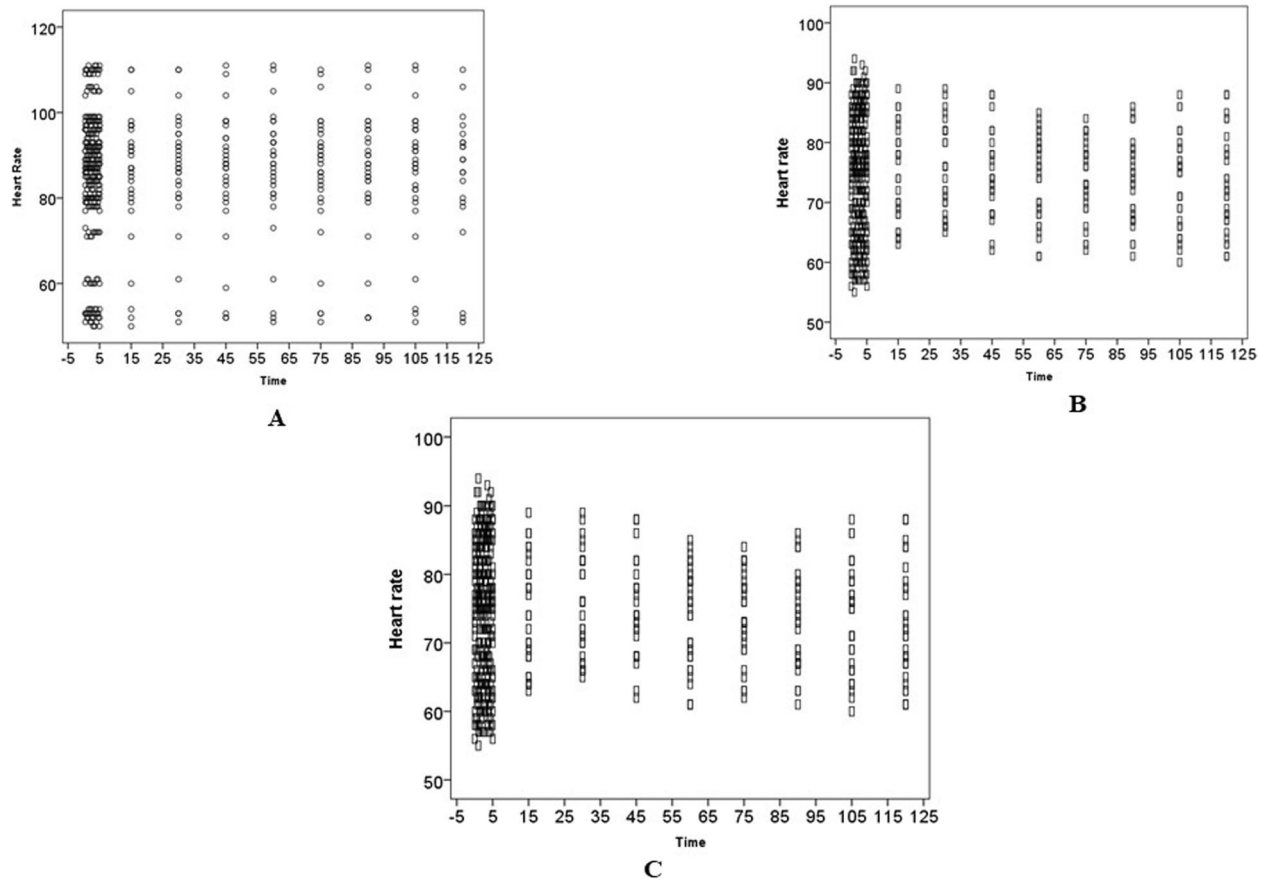

Fig. 2 Graph showing trends of heart rate in post-extubation period

found insignificant between group A and group C up to 2.5 min after which it became highly significant in group A ($P < 0.0001$) when compared to group B and group C. The SBP, DBP, and MAP remained comparable between group B and group C from the start of infusion up to extubation. Mean change in SBP, DBP, and MAP (Fig. 3) in the post-extubation period was significantly higher in group A when compared to group B ($P < 0.0001$). It was more significant in group A than in group C ($P < 0.0011$) but was found insignificant between group B and group C ($P = 0.22$).

In comparison, the mean SpO2 was comparable at the start of dexmedetomidine infusion up to extubation in all three groups. Time to extubation was 8.60 ± 0.51 min in group A, 8.83 ± 0.51 min in group B, and 9.34 ± 0.48 min in group C, respectively ($P = 0.058$) (Table 2).

The sedation score in group A was found to be the least of all the three groups. It was found to be the highest in group C patients. However, sedation scores after 1 h were found to be comparable in all the groups (Fig. 4).

Discussion

The incidence of complications post-extubation is three times higher in frequency than those occurring during intubation (Howell et al. 2004; Antony et al. 2016; Charlson et al. 1990). Dexmedetomidine being an alpha-2 (α-2) agonist depresses the sympathoadrenal reflex and thereby mitigates the hemodynamic response during these events (Manne et al. 2014; von Delius et al. 2009; Keniya et al. 2011). It causes sedation and provides smooth extubation (Aksu et al. 2009a). It attenuates the gag reflex which results in better tracheal tolerance in comparison with other drugs used for sedation.

The recommended dose for using dexmedetomidine has been 0.1 to 1 μg/kg/h. The incidence of hypotension is more than half during the use of dexmedetomidine for sedation (Talke et al. 2000). In studies where higher rates of infusion were used, there were more incidences of adverse effects like hypotension and bradycardia (Shruthi et al. 2016). One of the latest studies suggests that the stress response to direct laryngoscopy and endotracheal intubation can be attenuated successfully and without

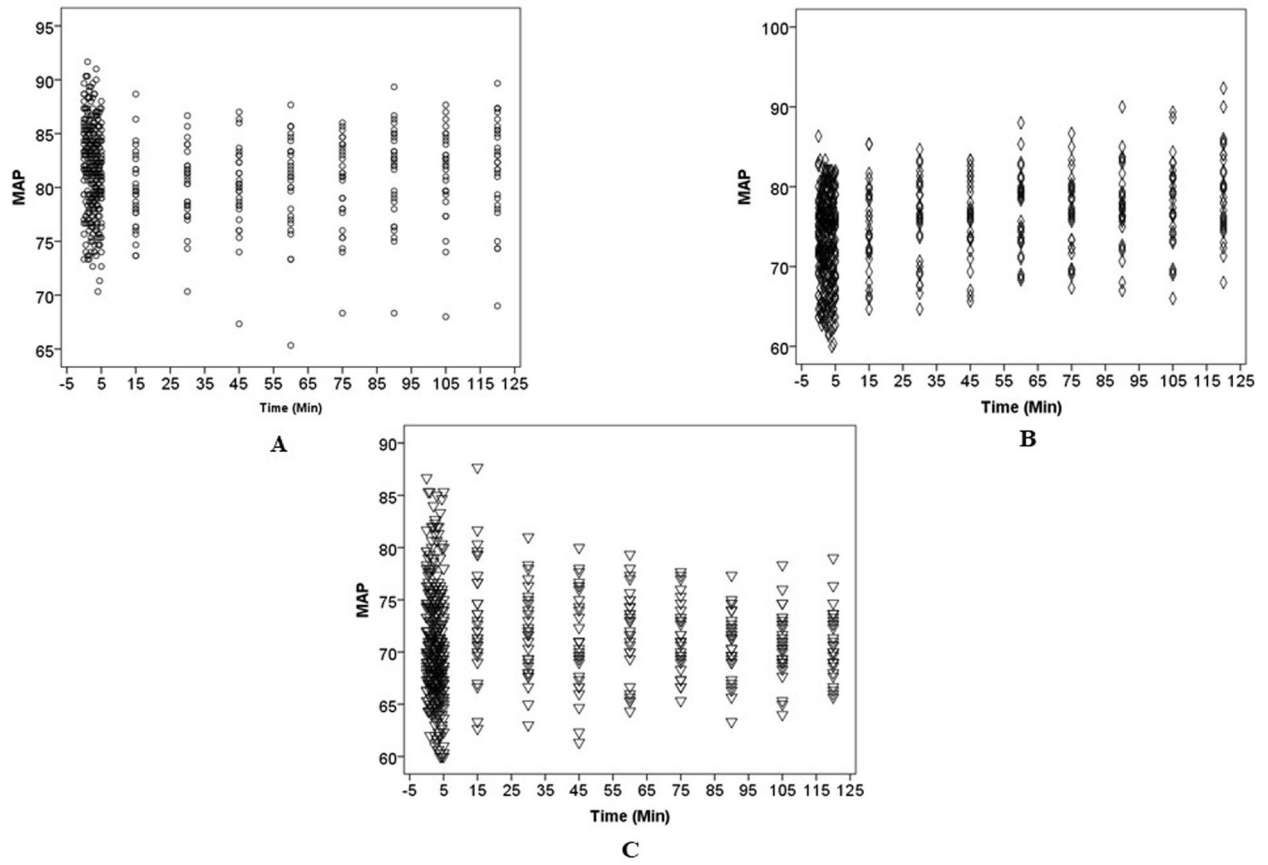

Fig. 3 Graph showing trends of MAP in post-extubation period

any side effects using nebulization of dexmedetomidine (Kumar et al. 2020).

In our study, the main objective was to find the optimal dose of dexmedetomidine which can be used to attenuate the extubation response in chronic smokers as we are well aware of the exaggerated upper airway reflex among smokers. The optimal dose is defined as the one which provided stable hemodynamics both during and post-extubation while improving the extubation quality.

Talke et al. (Talke et al. 2000) concluded that the hemodynamic stress response to extubation was less, and the quality of extubation was improved when dexmedetomidine was used. Luthra et al. (Luthra et al. 2017) and Khan et al. (Khan et al. 1999) in their study using dexmedetomidine infusion (0.2 μg/kg/h and 0.4 μg/kg/h) found a significant reduction in MAP and HR before and up to 10 min post-extubation. Similarly, in our study, dose of 1 μg/kg (group C) had a higher incidence of bradycardia than the dose of 0.5 μg/kg (group A) and 0.75 μg/kg (group B). Bradycardia (*HR* < 50 beats/min) was seen in a single patient in group A, two patients in group B, and nine patients in group C, respectively. The α-2 receptors have a role in regulating the autonomic and cardiovascular response systems, and their activation leads to sedation, reduction of sympathetic outflow, and augmentation of cardio-vagal activity which explains the attenuation of heart rate when used. Also, α-2 receptors within the spinal cord play a role in modulating pain pathways resulting in mild analgesia (Bloor et al. 1992; Ebert et al. 2000).

In our study, we infused dexmedetomidine over 10 min before extubation. The MAP just before extubation was 97.87 ± 3.6 mm of Hg in group A, 84.73 ± 6.49 mm of Hg in group B, and 81.17 ± 6.6 mm Hg in group C, all within the normal limits. This shows that the transient presser phase can be attenuated by using a slower and prolonged infusion. It is important to maintain MAP within the accepted limits as chronic smokers are often associated with higher autoregulation values of cerebral and renal perfusion (Varon and Marik 2008). Hypotensive episodes during the perioperative period can have a significant bearing on the outcomes of the patients (Lapage and Wouters 2016). Hypoperfusion due to a decrease in blood pressure can affect vital organs like the

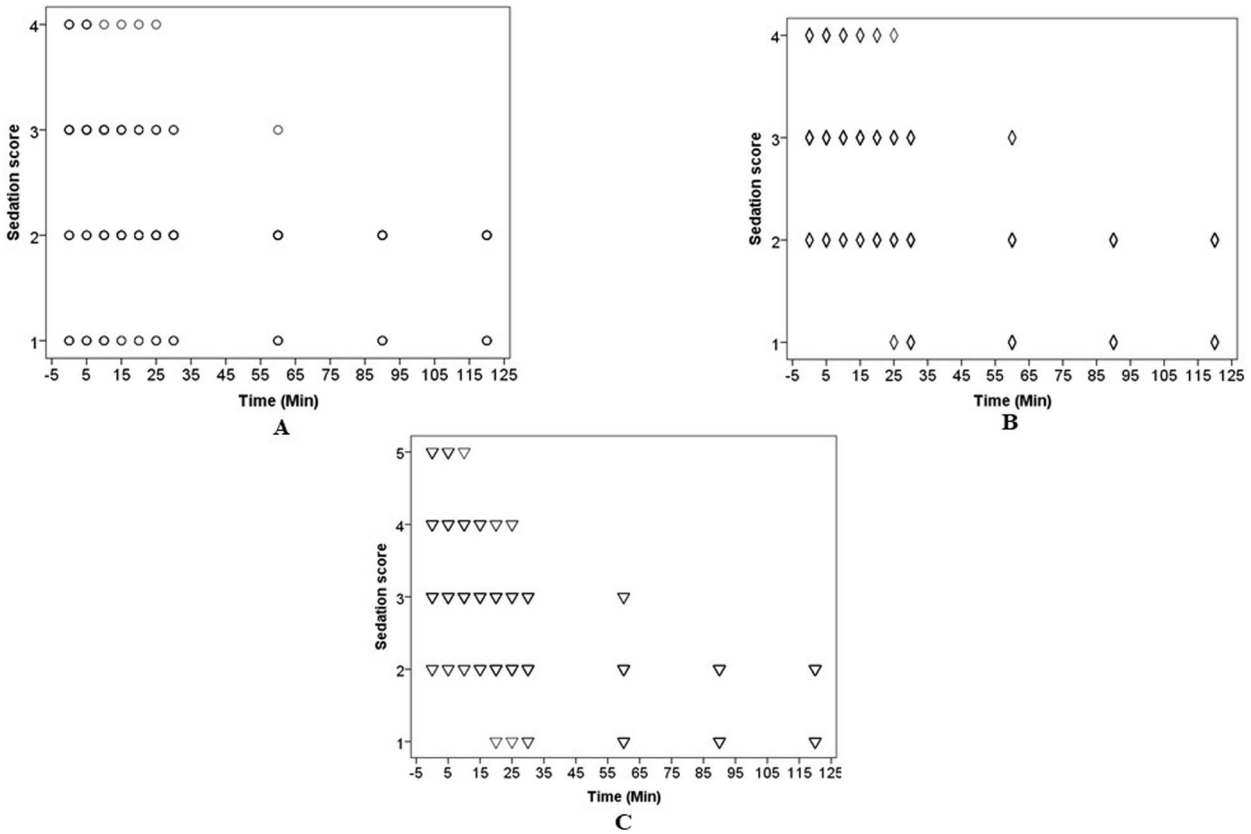

Fig. 4 Graph showing trends of postoperative sedation scores

brain and kidneys. In our study, MAP in all patients was above 65 mm Hg, as has been observed in the study conducted by S. R. Prasad et al. (Prasad et al. 2012).

It was observed in our study that 60% of patients in group C had no coughing during extubation in comparison with 46.6% and 16.6% of patients in group B and group A. Minimal coughing was found in 40% of patients in group B as compared to 30% and 26.6% found in group C and group A. Another study by Aksu et al. (Aksu et al. 2009b) done in patients undergoing rhinoplasty concluded that dexmedetomidine was better than fentanyl in controlling airway reflex responses encountered during extubation and maintaining hemodynamic stability. Fan et al. (Fan et al. 2015) concluded that 0.7 μg/kg of dexmedetomidine resulted in smoother extubation when compared to a 0.5 μg/kg dose.

Bindu et al. (Bindu et al. 2013) used a 0.75 μg/kg infusion of dexmedetomidine 15 min before extubation and found that it facilitates smooth extubation. In a study done by Antony et al. (Antony et al. 2016), they found similar results in 90% of patients with 0.5 μg/kg dexmedetomidine infusions, 93.3% of patients with 1 μg/kg dexmedetomidine infusion, and 16.7% of patients with saline infusion were smoothly extubated. Dexmedetomidine infusion causing the reduction in episodes of agitation in patients during emergence after nasal surgery has been ascertained in a study conducted by Garg et al. (Garg et al. 2018). Hence, we also conclude that in our study, the extubation quality is smooth and better with the dose of 0.75 μg/kg and 1 μg/kg in comparison with 0.5 μg/kg dexmedetomidine.

The sedative action of α-2 agonist depends on the dose of the drug, and the peak effect is attained after 45–60 min of administration of the drug. In our study, sedation score was maximum in group C (dexmedetomidine 1 μg/kg) and minimum in group A (dexmedetomidine 0.5 μg/kg), but after 1 h, they were comparable in all the three groups. It is pertinent to mention that all patients in our study were easily arousable, and none was deeply sedated, and no one required any intervention. Similar findings have been noticed in other studies with dexmedetomidine (Bindu et al. 2013; Kothari et al. 2014; Rani et al. 2016). As the elimination half-life of dexmedetomidine is 2 h, it is advisable to observe patients for 120 min to ensure patient safety.

This study aimed to evaluate the effect of dexmedetomidine in preventing extubation response in chronic smokers and thereafter to look for any adverse effects that might be associated with the drug. Quality of extubation was better with dexmedetomidine when used in a dose of 0.75 μg/kg and 1 μg/kg. However, while using 1 μg/kg, incidence of bradycardia was higher. Prolonged sedation was also seen with a 1 μg/kg dose of dexmedetomidine.

Not having a control group while comparing attenuation of extubation response among three groups was the major limitation of our study. We recommend more studies be done with a larger study population to authenticate our study.

Conclusions

In our study, we conclude that dexmedetomidine when used in a dose of 0.75 μg/kg and 1 μg/kg more effectively attenuates the hemodynamic response to extubation. However, a higher incidence of bradycardia was recorded using a 1 μg/kg dose of dexmedetomidine. Hence, we conclude that dexmedetomidine intravenous infusion at the rate of 0.75 μg/kg can be safely started 10 min before extubation. This reduces the extubation stress response in chronic smokers while providing stable hemodynamics during and after extubation.

Abbreviations

HR: Heart rate; NIBP: Noninvasive blood pressure; SpO2: Oxygen saturation; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; MAP: Mean arterial pressure; N2O: Nitrous oxide; OT: Operation theater; ETCO2: End-tidal carbon dioxide; Inj.: Injection; n: Number; RSS: Ramsay Sedation Scale.

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Authors' contributions

The authors read and approved the final manuscript. DS, study design and data analysis.VC, data collection and correspondence. AT, patient recruitment. JS, overall guidance. AG, checking for plagiarism and drafting. AS, literature review

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate:

After approval of the Dr. RPGMC Institutional Ethics Committee No. HFW-H-DRPGMC/***Ethics/2017-58*** dated 08/01/2017, our research was conducted in accordance with the Declaration of Helsinki. The trial is registered in Clinical Trials Registry (CTRI/2019/08/020728 dated 24 August 2017). The authors certify that they have obtained all appropriate patient consent forms (written). In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Consent for publication

NA

Competing interests

The authors declare that they have no competing interests.

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