A Randomised Controlled Trial of 0.5 Mcg / Kg and 1 Mcg/Kg of Dexmedetomidine on Attenuation of Haemodynamic Response to Extubation among Patients Undergoing Elective Surgeries

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Abstract: *Background: Endotracheal extubation elicit a strong sympathoadrenal response with potentially fatal implications in individuals with cardiovascular and cerebrovascular illnesses. To counteract this reaction, a variety of pharmacological treatments have been used. Aim: To compare the clinical effectiveness of two different doses of dexmedetomidine (0.5μg/kg versus 1μg/kg) for attenuation of cardiovascular response to extubation in patients undergoing major surgeries. Material and Method: Study Design: This was a single centre, hospital (in - patient) based, parallel - group, 1: 1, double - blind, active - controlled, randomised control study conducted by enrolling a total of 120 participants (60 participants in each group). The haemodynamic parameters: Heart Rate, Blood Pressure and side effects were measured in both the groups. Results: The mean 'time for extubation' among the participants in the 0.5μg/kg and 1μg/kg group were 491 and 542 seconds, respectively. The pressor reflex was more effectively attenuated among the participants given 1 μg/kg in comparison to participants given 0.5μg/kg of Dexmedetomidine. The incidence of side effects viz. sedation, hypotension and bradycardia were significantly higher among the participants given 1 μg/kg of Dexmedetomidine. Conclusion: Dexmedetomidine in dose of 1μg/kg attenuate the pressor reflex more effectively. High dosage of Dexmedetomidine was also associated with higher incidence of side effects.*

Keywords: Extubation, Dexmedetomidine

1. Introduction

The founding pillars of anaesthesia are to provide smooth induction, haemodynamic stability, and best operative conditions [1, 2]. The increase in blood pressure during surgery can result in increased bleeding or oedema in the operative field [1]. Similarly, hypertension during the postoperative period can also cause a hematoma. For an exceedingly long time now, airway management by laryngoscopy, endotracheal intubation (LETI), extubation, and emergence during general anaesthesia are known to induce clinical changes in haemodynamic variables

Although the 'pressor' response to extubation is of shorter duration, it nevertheless, put significant detrimental effects on the coronary and cerebral circulation. For most patients, the pressor reflex is easily tolerated [4]. However, among a subgroup of patients, including those with a present or history of cardiac ailments including atherosclerosis, hypertension, myocardial infarction, and cerebrovascular diseases including aneurysms and tumours, are at tremendous risk of adverse outcomes [3 - 5]. Furthermore, geriatric patients make up an increasingly substantial percentage of the inpatient population [6]. These patients have abnormal cardiovascular parameters (most importantly elevated blood pressure), placing them at increased risk of MI, stroke, congestive heart failure (CHF), or unfortunately sudden death [3 - 5].

Thus, it only seems logical and desirable that minimizing these physiologic challenges before - , during - , and after the surgery is in the best interest of the patient. Studies support the hypothesis that controlling perioperative stress improves outcomes, particularly among high - risk patients [7]. Several classes of pharmacological agents have been evaluated to attenuate the haemodynamic responses to extubation.

Dexmedetomidine is a highly selective α2 – adrenoreceptor agonist. In addition, dexmedetomidine has sedative, analgesic, amnestic and sympatholytic, properties, however, it does not cause pulmonary depression [8 - 10]. We, therefore, conducted this study intending to determine and evaluate the effectiveness of two different doses of dexmedetomidine (0.5μg/kg versus 1μg/kg) in maintaining haemodynamic stability during extubation among patients undergoing major abdominal surgery under general anaesthesia.

2. Literature Survey

Slogoff and Keats., reported that most ischemic episodes during anaesthesia were associated with intubation and extubation simulation [3]. During intubation and extubation, the increased haemodynamic response is seen secondary to reflex activation of the sympathetic nervous system which supplies the greater part of the upper airways [4]. Gupta et al stated that use of dexmedetomidine improved haemodynamic stability following airway manipulation. [13]

3. Material and Methods

Study Design: This was a single centre, hospital (in - patient) based, parallel - group, 1: 1, double - blind, active - controlled, randomised control study.

Study Settings: The present study was conducted at the Department of Anaesthesiology, Sawai Man Singh Medical College, and affiliated hospitals, Jaipur, Rajasthan.

Study Outcomes: Heart Rate, Blood Pressure (Systolic - , Diastolic - , and Mean arterial Pressure), and the incidence of the following side effects: cough, agitation, shivering, Postoperative Nausea & Vomiting (PONV), hypotension, bradycardia, respiratory depression, bronchospasm, and laryngospasm.

Ethical consideration: Study was approved by the institutional ethical committee - biomedical research of SMS Medical college, Jaipur.

Study groups: The participants were divided into the following study groups using block randomization:
1) **Group I (Intervention/Treatment group):** Intravenous infusion of dexmedetomidine 1µg/kg over 10 minutes at the time of emergence.
2) **Group C (Control group):** Intravenous infusion of dexmedetomidine 0.5 µg/kg over 10 minutes at the time of emergence.

Participants' recruitment: The participants were recruited into the study after verifying that they fulfilled the following selection criteria.

Inclusion Criteria: Patients who were scheduled for any type of major abdominal surgery requiring General Anaesthesia for 1 - 3 hours of duration, all genders, between age 18 - 55 years of age**,** ASAClass I & II and patients who gave written, informed consent to take part in the study.

Exclusion Criteria: Pregnant women**,** Obese patients [BMI$\geq$ 30.0]**,** Patients with Cardiopulmonary and neuropsychiatric comorbidities, Laparoscopic surgeries**,** Patient with an allergy to dexmedetomidine, patient refused to take part in the study.

Sample Size Calculation: To calculate the minimum required sample size for the study, we employed the formula recommended by Zhong B, (2009) for a randomised control trial [11]. Using the formula for randomised control trial, the minimum required sample size for the study was calculated as 120 (60 participants in each group).

Informed Consent: All the questions from participants about the study, drug, procedure, risk, and data privacy were answered. The participants were informed and explained that they have the right to withdraw from the study at any point in time. Thereafter, willing participants were asked to sign the consent form. **Randomization and Allocation Concealment:** The participants were randomly assigned to either the intervention or control group using a computer - generated programme based on a permuted block design (n=6). The details of the allocated groups were concealed from the principal investigator and research team by supplying random numbers in opaque and sealed envelopes.

Blinding: This was a double - blind study, whole team involved in surgery (including surgeon, anaesthesiologists, and nurses) and the study participants were blinded by the intervention & control groups.

Data Collection: The data were collected in an electronic tablet - based application by the principal investigator.

Plan and procedure
1) Pre anaesthetic evaluation done one day prior to surgery. Monitors were attached to measure the vital parameters viz. pulse rate, non - invasive blood pressure, pulse oximetry, ecg, and body temperature during the peri - operative period
2) Ringer lactate at the rate of 8ml/kg/hr, iv metoclopramide 0.1mg/kg, iv glycopyrrolate 0.004mg/kg, iv midazolam 0.02mg/kg were given as preanaesthetic medication, patients preoxygenated for 3 min with 100% O2. Induction done with iv propofol 2mg/kg and iv scholine 2mg/kg and patient was intubated with appropriate size ET tube. Maintenance was done with N2O in O2 2: 1, sevoflurane 1 - 3% and atracurium as needed.
3) At the end of surgery anaesthesiologist stopped sevoflurane and nitrous oxide and fresh gas flow was increased from 3 to 6 L/min. This time was noted as time 'zero' or 'emergence'. Thereafter, the drug was given (either intervention or control) to the participants in a pre - specified manner over ten minutes.
4) Injection ondansetron 4mg iv, suction of orogastric region done, iv neostigmine 0.05mg/kg, iv glycopyrrolate 0.01mg/kg given. Extubation was performed when the patient was fully responsive, regained muscle power (tested by grasping the hand) and started following verbal commands.
5) The SBP, DBP, MAP, SPO2, and HR were recorded at the time of emergence and then every 2 minutes until extubation. Thereafter the prespecified vitals were recorded at the time of extubation at 1, 3 and 5 min post - extubation, and thereafter every 5 min till 30 minutes post - extubation and lastly at 45 and 60 min post - extubation.
6) The time required for extubation and sedation scores were noted.

Statistical analysis: Comparison of continuous variables with baseline values was analysed using a student's t - test in each group. Categorical variables were analysed using chi - square (χ^2) or Fisher definite probability tests. A *P* - value

< 0.05 was considered statistically significant. **Funding:** The present study did not receive any funding.

4. Results

To recruit the participants for the present study, the author screened a total of 157 patients undergoing major abdominal surgery at the institute. Out of the total 157 patients: 28 (17.8%) were excluded using selection criteria and 9 (5.7%) participants refused to participate in the study and the remaining 120 (76.4%) patients were enrolled in the present study. There were no losses to follow - up or deaths and the data of all enrolled 120 patients were analysed as part of this study. [12].

Table 1: Descriptive parameters of study participants (n = 154)

Variable	Group		P - value
	A (n, %)	B (n, %)	
Age, Mean (SD)	48.0 (12.07)	46.633 (13.57)	0.547
Gender			
Male	33 (55.0)	28 (46.7)	0.3612
Female	27 (45.0)	32 (53.3)	

ASA Grade			
I	27 (45.0)	28 (46.7)	0.845
II	33 (55.0)	32 (53.3)	
BMI			
Overweight	**41 (68.3)**	**39 (63.3)**	0.087
Mean BMI	26.12 (2.67)	26.26 (2.8)	0.974
Time for Extubation (seconds)			
Mean	491.8 (59.98)	542.7 (57.84)	< 0.0001
Range	377 – 623	434 - 674	-

Figure 1 shows the trend in heart rate among the participants in the intervention and the control group throughout the study. At the time of emergence, the difference in the mean heart rate among the participant in the group C (73.8) and group I (71.3) was statistically insignificant (p=0.058). However, as the study progressed, the difference in the heart rate between the participants in the two groups became more apparent. At the time of extubation, the heart rate among the participants in the control group was significantly higher (73.5) in comparison to the intervention group (68.3; p - value = 0.009). Also, the difference in heart rate among the two groups was significant on multiple occasions viz. at 1, 3, 5 and 10 minutes after the extubation.
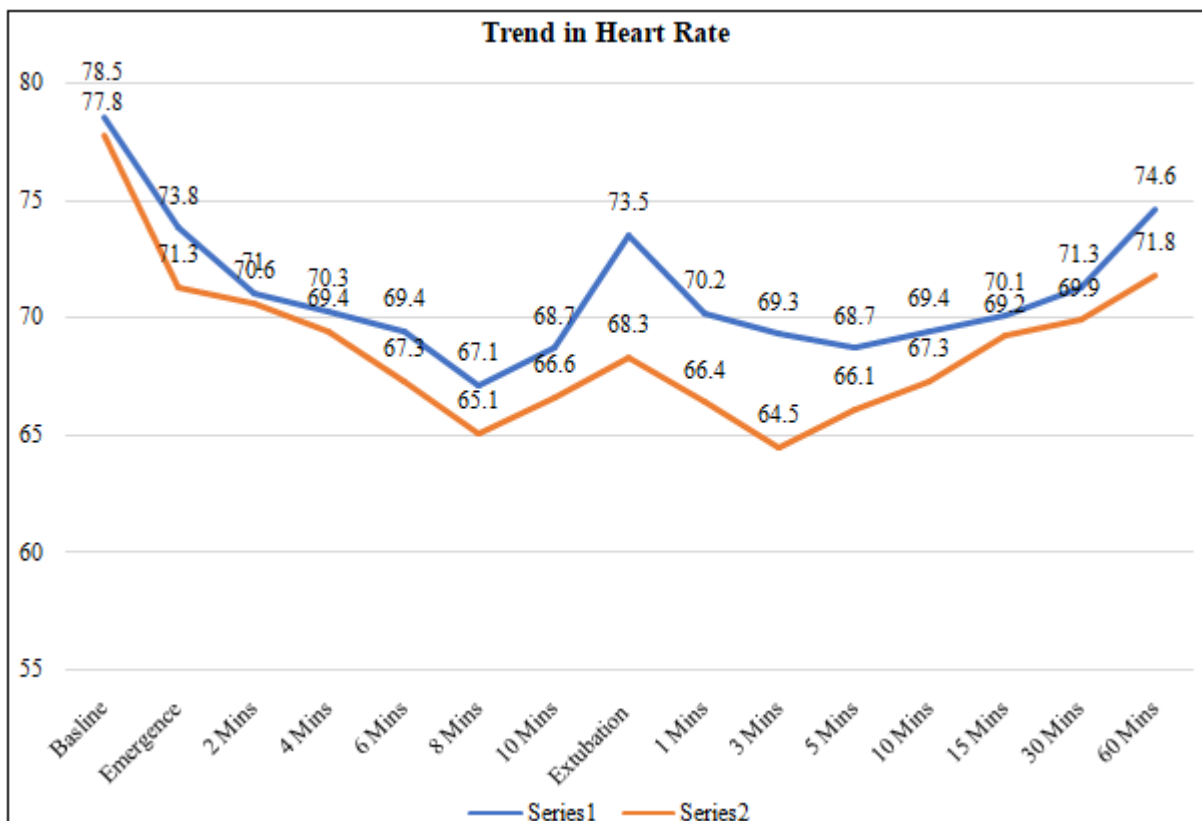

Figure 1: Change in Heart Rate over time among study participants

Figure 2 shows the trend in mean arterial pressure among the participants in the intervention and the control group throughout the study. At the time of emergence, the mean MAP among the participant in the group C (86.2 mm Hg) was slightly higher than group I (84.5 mm Hg). At the time of extubation, the MAP among the participants in the control group (86.6 mm Hg) was significantly higher in comparison to the intervention group (81.4 mm Hg). The difference in the MAP among the participants in the control group and the intervention group was statically insignificant at baseline (p=0.61) and emergence (p=0.063). However, the difference in MAP among the two groups was statistically significant at the time of extubation (p= 0.019) and all time points viz.1, 3 5, 10, 15, 30, and 60 minutes after the extubation.

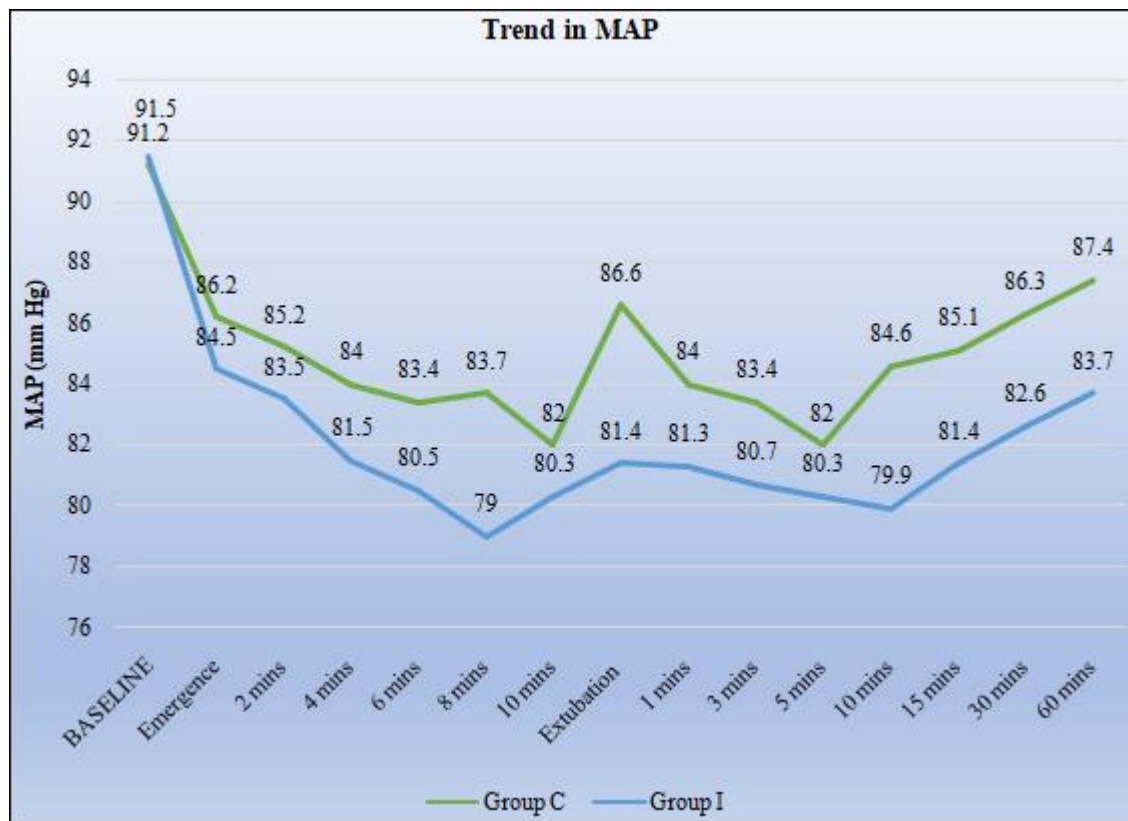**Figure 2:** Change in the Mean Arterial Pressure from the baseline during the period of study

Overall, 15.0% and 35% of participants in the control and intervention group respectively had at least one episode of hypotension during observation (p=0.011). Overall, 11.7% and 31.7% of participants in the control and intervention group respectively had at least one episode of bradycardia during observation (p=0.008). None of the participants in either the intervention or control group had an incidence of any severe side effects. In the present study, we measured the sedation score at the time of extubation, 30 minutes, and 60 minutes after extubation. At the time of extubation, participants in the control group were less sedated in comparison to participants in the intervention group. After 30 minutes of extubation, participants in the control group were still less sedated than participants in the intervention group D. The distribution of the sedation score in the two groups was statistically highly significant (p<0.001) both at the time of extubation and thirty minutes after extubation.

Table 2: Distribution of study participants based on the sedation score (n=120)

Sedation Score	Sedation Score			
	At Extubation		After 30 Minutes	
	C (n, %)	I (n, %)	C (n, %)	I (n, %)
1	0 (0.0)	0 (0.0)	5 (8.3)	0 (0.0)
2	0 (0.0)	0 (0.0)	31 (51.7)	4 (6.7)
3	13 (22.0)	0 (0.0	19 (31.7)	22 (36.7)
4	24 (40.7)	1 (1.7)	4 (6.7)	19 (31.7)
5	16 (27.1)	21 (35.0)	1 (1.67)	12 (20.0)
6	6 (10.2)	26 (43.33)	0 (0.0)	3 (5.0)
7	0 (0.0)	12 (20.0)	0 (0.0)	0 (0.0)
	Pearson chi2) = 59.6 P value < 0.001		Pearson chi2= 48.14 P value < 0.001	
Median	4	6	2	3

5. Discussion

Airway manipulation during endotracheal extubation causes sudden sympathetic nervous system stimulation and catecholamine release [6, 7]. To lessen the haemodynamic reactions to extubation, several kinds of pharmaceutical drugs have been investigated. Alpha - 2 agonists such as clonidine and dexmedetomidine have emerged as front - runners for attenuating the "pressor" response to extubation across all medication classes, thanks to their pharmacological profile. We predicted that higher doses of dexmedetomidine would be more effective than low doses at preventing variations in haemodynamic parameters before, during and after extubation without significantly increasing the likelihood of side effects.

In the present study, we observed that the heart rate declined in both the low - and high - dose group after the infusion of Dexmedetomidine. This decline was observed immediately after infusion, at emergence, and continued up until just before extubation. There was an abrupt increase in HR immediately following the extubation. Just before extubation, the HR was 12% and 14% lower than the baseline among the participants in the control and the intervention group. At the time of extubation, the HR was 6% and 12% lower than the baseline among the participants in the control and the intervention group. Thus, the HR fluctuated to a lesser degree among the participants given higher doses of Dexmedetomidine. Therefore, Dexmedetomidine in both lower and higher doses effectively attenuated any abrupt increase in HR higher than baseline values.

Following extubation, a decline in HR was noted in both groups. At 1 - , 5 - , 10 - , and 30 minutes after extubation the HR was 10%, 12%, 10% and 9% below the baseline values among the control group. At 1 - , 5 - , 10 - , and 30 minutes after extubation the HR was 14%, 15%, 13% and 10% below the baseline values among the intervention group. As time passed, the drug in the system was metabolised, hence its effect on HR declined. This explains the gradual return of HR to near baseline values in both the intervention and the control group after extubation. In the present study, at the end line, the HR among the participants in the control and intervention groups was 5% and 7% below the baseline values.

Similar to our findings, Gupta et al. (2016) reported that multiple comparisons between groups showed that the heart rate in patients given 1 mcg/kg of Dexmedetomidine was significantly less than that in patients given 0.5 mcg/kg Dexmedetomidine at all times [13]. Shamin et al. reported that the HR was significantly ($P < 0.05$) higher among patients given Normal Saline as compared to Groups B (1 mcg/kg) and group C (0.7 mcg/kg) during and after extubation [14]. However, the HR values were comparable throughout the perioperative phase in Groups B and C. Scheinin *et al.* concluded from their study that dexmedetomidine attenuates sympathoadrenal responses to intubation and extubation [15]. Tanskanen *et al.* conducted a double - blind study and concluded that dexmedetomidine increased the perioperative haemodynamic stability, and extubation was faster without respiratory depression [16]. Bhardwaj et al., (2020) reported that the mean HR at peak concentration of dexmedetomidine was 82.23, 73.57, and 62.77 bpm in Groups A, B, and C, respectively ($P < 0.001$) [17]. Further, they reported that during and after extubation, HR, were higher with low-dose dexmedetomidine (0.5 μg/kg) as compared to the higher doses (0.75 μg/kg or 1 μg/kg) [17]. Similar to our study, they also reported that during the post - extubation period, all the haemodynamic parameters were decreased more among the participants given higher doses.

In the present study, we observed that all three indices of blood pressure viz. SBP, DBP, and MAP showed almost similar trends from baseline to end line among the participants in the two groups. Collectively, the mean BP values declined to a greater extent among patients given higher doses (1 mcg/kg) of Dexmedetomidine in comparison to lower (0.5mcg/kg) of Dexmedetomidine. Moreover, the degree of fluctuations in the BP during the study period was of less intensity among given higher doses (1 mcg/kg) of Dexmedetomidine in comparison to lower (0.5mcg/kg) of Dexmedetomidine.

In the present study, we observed that the MAP declined in both the low - and high - dose group after the infusion of Dexmedetomidine. This decline was observed immediately after infusion, at emergence, and continued up until just before extubation. There was an abrupt increase in MAP immediately after the extubation. Just before extubation, the MAP was 10% and 12% lower than the baseline among the participants in the control and the intervention group. At the time of extubation, the MAP was 5% and 11% lower than the baseline among the participants in the control and the intervention group. Thus, the MAP fluctuated to a lesser degree among the participants given higher doses of Dexmedetomidine.

The difference in MAP among the two groups was statistically significant at the time of extubation (p= 0.019) and all time points viz.1, 3 5, 10, 15, 30, and 60 minutes after the extubation. Likewise, Gupta et al. reported that a decrease in the MAP after induction was observed in all patients, but the decrease in the mean arterial blood pressure was more profound in patients of group III (1 mc/kg), with a highly significant difference ($P < 0.001$) [13]. However, Shamim et al., reported that the MA*P* values were statistically insignificant and comparable throughout the perioperative phase in Groups B (1 mcg/kg) and group C (0.7mcg/kg) [14]. Bhardwaj et al. reported that during and after extubation, SBP, DBP, and MAP were higher with low-dose dexmedetomidine (0.5 μg/kg) as compared to the higher doses (0.75 μg/kg or 1 μg/kg) [17]. Yildiz *et al.* [18] and Keniya *et al.* [19] studied the effect of dexmedetomidine on the haemodynamic responses to intubation and extubation. They both concluded that the increase in blood pressure and heart rate was significantly lower in the dexmedetomidine group than in the placebo group.

Another study conducted by Sulaiman *et al.* also found a statistically significant difference in the SBP, the DBP, and the MAPs at the first, the third, and the fifth minutes after extubation between the dexmedetomidine group and the control group [20]. Bajwa *et al*. showed a decrease in BP and HR by administering intravenous 1 mcg/kg dexmedetomidine at intubation and extubation [21]. Ye Q et al. reported that intravenous infusion of dexmedetomidine 0.4μg/kg before induction could not effectively inhibit the stress response, but dexmedetomidine 0.6μg/ kg and 0.8μg/kg could effectively restrain the intubation reaction, attenuate the intraoperative stress response, and maintain the haemodynamic stability during extubation [22]. Manne GR et al. found that dexmedetomidine in the dose of 0.2 or 0.4 μg/ kg/h reduces the stress response during intubation and extubation, and the latter was better for maintaining haemodynamic stability with no significant changes in the incidence of bradycardia and hypotension [23].

The extension of the pharmacological actions of Dexmedetomidine is responsible for its both common and severe side effects. Two of the most common side effects on the cardiovascular system include bradycardia and hypotension. In the present study, we observed that 15.0% and 35% of participants in the control and intervention groups had at least one episode of hypotension during observation (p=0.011). Yavascaoglu B et al reported that the incidence of hypotension was significantly higher in the 0.75 μg/kg group than that in the 0.5μg/ kg group [24]. Manne GR et al. reported that dexmedetomidine in the dose of 0.2 or 0.4 μg/ kg/h reduced the stress response during intubation, and maintained haemodynamic stability with no significant changes in the incidence of hypotension [23]. Ye Q et al., also reported that the prevalence of hypotension among groups D1, D2, and D3 was 20%, 10%, and 6.69%, respectively [22]. Sebastian et al. reported that none of the participants in any group had even a single incident of hypotension [25]. Gupta et al. reported that hypotension was not observed in any

patient in any group during the study period [13] . These adverse effects are more marked in hypovolemic patients, the elderly, diabetes mellitus, or chronic hypertension.

In the present study, 11.7% and 31.7% of participants in the control and intervention groups had at least one episode of bradycardia during observation (p=0.008). Inhibition of the function of the atrioventricular node and the sinoatrial node, lowering of the catecholamine level in the blood, and activation of the vagus nerve by dexmedetomidine are all factors that have been linked to the development of bradycardia. Thus, it is believed that these effects are more prominent among those receiving higher doses of Dexmedetomidine. Yavascaoglu B et al reported that the incidence of bradycardia was significantly higher in the 0.75 μg/kg group than that in the 0.5μg/ kg group [24] . Ye Q et al. observed that dexmedetomidine can reduce fluctuations in heart rate (HR) and blood pressure (BP) during extubation, with the optimal benefit occurring at a dose of 0.4μg/kg and the lowest incidence of bradycardia, however, dexmedetomidine in the dose of 0.8μg/kg dramatically increased the incidence of bradycardia [22] . Seo KH et al. also found that the incidences of bradycardia at 0.75μg/kg and 1μg/kg increased compared with that at 0.5μg/kg, which was consistent with our finding [26] .

6. Conclusion

In summary, both a low dose of dexmedetomidine (0.5 mcg/kg) and a high dose of dexmedetomidine (1 mcg/kg) significantly reduced the intensity of pressor response, defined as a sudden increase in heart rate and blood pressure upon extubation. However, the subjects who were given higher dosages of dexmedetomidine experienced less variation in their cardiovascular parameters viz. heart rate and blood pressure. People who were given higher doses of dexmedetomidine were more likely to have bradycardia and hypotension, although this difference did not reach statistical significance. Last but not least, the patients who were given greater doses of dexmedetomidine were more sedated, which resulted in a longer delay until they were extubated.

7. Future Scope

This study will help in acquiring better perioperative outcome. Although placebo group was not used which is a limitation of this study.

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