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ORIGINAL INVESTIGATION

Comparison between dexmedetomidine and fentanyl bolus in attenuating the stress response to laryngoscopy and tracheal intubation: a randomized double-blind trial

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Laryngoscopy;
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Abstract
Background and objectives: Laryngoscopy and tracheal intubation lead to a sympathoadrenal response. We compared the efficacy of dexmedetomidine with fentanyl bolus to attenuate this response.
Methods: One hundred patients admitted for routine surgical procedures under general anesthesia were enrolled in this double blind, randomized, controlled study. Patients were randomly assigned to two groups: Group F received injection of fentanyl 2 $\mu g.kg^{-1}$ and Group D received injection of dexmedetomidine 0.5 $\mu g.kg^{-1}$ diluted up to 5 mL by adding normal saline intravenously over 60 seconds. Five minutes thereafter, following induction with propofol and vecuronium, tracheal intubation was performed after 3 minutes of mask ventilation. Hemodynamic parameters were observed at an interval of 2 minutes before tracheal intubation and at an interval of 1 minute for 5 minutes after tracheal tube cuff inflation. Continuous variables are presented as mean with 95% confidence interval, and *t*-test was applied for comparing the difference of means between two groups after checking the normality condition. Chi-square test was applied to test the independence of attributes of categorical variables. Repeated measures two-way ANOVA was performed to compare the outcome variables between the two groups.
Results: The difference in heart rate and mean arterial pressure of patients in two groups after laryngoscopy and intubation was not statistically significant at any point of time. The hemodynamic changes did not require any intervention in the form of administration of rescue medication.
Conclusions: Dexmedetomidine 0.5 $\mu g.kg^{-1}$ is as effective as fentanyl 2 $\mu g.kg^{-1}$ in attenuating the hemodynamic response accompanying laryngoscopy and tracheal intubation.
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Introduction

Laryngoscopy and tracheal intubation lead to tachycardia and hypertension due to increase in the plasma concentration of catecholamines subsequent to sympathetic stimulation. The elevation in arterial pressure generally peaks in 1–2 minutes and returns to normal levels within five minutes.[1] This may be inconsequential in normal people but may lead to serious morbidity in patients with coexisting cerebrovascular or cardiovascular conditions.[2] The laryngoscopic response in these patients can increase myocardial oxygen demand and may lead to complications in susceptible individuals.

Various prophylactic interventions have been tried to blunt this stress response; administration of local anesthetics, opioids, beta blockers, alpha 2 [α2] adrenergic agonists, vasodilators, magnesium, or increased concentrations of volatile anesthetic.[3]

Fentanyl is a narcotic with quick onset and short duration of action and is used as a component of balanced general anesthesia. Fentanyl attenuates this hemodynamic stress response by its action on opioid receptors and by decreasing sympathetic outflow.

Dexmedetomidine is a newer α2 receptor agonist having eight times higher affinity and α2 selectivity as compared with clonidine. Dexmedetomidine attenuates these potentially harmful cardiovascular reactions during induction of anesthesia and has been used in infusion for this purpose.[3–6] However, a prolonged induction of anesthesia is not desirable.[7]

There has been an interest in evaluating the effect of dexmedetomidine on the airway reflexes and hemodynamics during tracheal extubation following general anesthesia also. The findings suggest that a single-dose bolus injection of dexmedetomidine administered over 60 seconds, 5 minutes before tracheal extubation, attenuates airway-circulatory reflexes safely and effectively.[8,9]

We compared bolus dexmedetomidine 0.5 $\mu g.kg^{-1}$ with fentanyl 2 $\mu g.kg^{-1}$ for sympatholysis and attenuation of this hemodynamic response in patients with American Society of Anesthesiologists (ASA) physical status I and II. We postulated that the single-dose bolus of dexmedetomidine may possess the ability to obtund the hemodynamic response to laryngoscopy and tracheal intubation.

Methods

Ethics statement

This study was conducted after obtaining ethical clearance from the Institutional Review Board and was registered prior to patient enrollment (Trial code CTRI/2017/09/009857 available at http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=20262). Written informed consent was obtained from all the patients before enrolling them for the study. One hundred patients admitted for routine surgical procedures under general anesthesia, who were willing to participate and fulfill the inclusion criteria, were enrolled in this parallel group, non-inferiority, double blind randomized, controlled study. This study was conducted in a tertiary care university hospital during the period of December 2017 to November 2018.

Patients with ASA physical status I and II, between 18–50 years of age of either sex with airway of Mallampati grade I and II and willing to participate were included in the study. The exclusion criteria included pregnancy, morbid obesity, full stomach, emergency surgery, and any protocol violation by the participant. Patients in whom the duration of laryngoscopy lasted more than 25 seconds were also excluded.

After enrollment in the study, the patients were premedicated with alprazolam 0.5 mg and ranitidine 150 mg orally on the night before surgery. Preoperatively, baseline hemodynamic parameters were recorded. An intravenous access was established, and routine monitoring in the form of electrocardiography, pulse oximetry, and noninvasive arterial pressure were instituted. Simple randomization method was used to assign the patients into two groups using sequentially numbered, opaque, sealed envelope based on computer-generated random numbers. Allocation sequence generation, enrollment of the participants, and assigning participants to the trial groups were performed by different clinicians.

Group D received dexmedetomidine 0.5 $\mu g.kg^{-1}$ intravenous (IV) diluted up to 5 mL by adding normal saline intravenously over 60 seconds. Group F received fentanyl 2 $\mu g.kg^{-1}$ IV diluted up to 5 mL by adding normal saline intravenously over 60 seconds. Following 5-minutes of preoxygenation, patients were induced with propofol IV in a dose of 2 $mg.kg^{-1}$ body weight over 30 seconds, followed by vecuronium 0.1 $mg.kg^{-1}$ IV. After 3 minutes, tracheal intubation was performed with an appropriately sized cuffed tracheal tube.

Anesthesia was maintained with an inhalational agent along with controlled ventilation with nitrous oxide 66% and oxygen 33%. Surgical stimulation was not allowed for 5 minutes after intubation. Hemodynamic parameters (heart rate and mean arterial pressure) were observed at an interval of 2 minutes before tracheal intubation and at an interval of 1 minute for 5 minutes after tracheal intubation and cuff inflation. The rescue medication was atropine 0.3 mg if the heart rate was less than 50 bpm, or mephentermine 6 mg if the mean arterial pressure fell more than 20% of baseline.

The primary outcome measures were the efficacy of bolus administration of dexmedetomidine and fentanyl in attenuating the cardiovascular stress response (heart rate and mean arterial pressure) accompanying laryngoscopy and tracheal intubation. The secondary outcome was to look for any adverse effects of these interventions. A clinician not involved in the study prepared the study drugs. The patients and the clinician involved in data collection were not aware of the group allocation.

Statistical analysis

Since it was a parallel group, non-inferiority trial, the sample size was estimated considering a maximum of 10-unit difference of heart rate between test and control groups.[10] Assuming a standard deviation of 15 units and equivalence limits of 10 units of heart rate, i.e., difference in means of two groups is no more than 10 units, the study required a sample size of 49 for each group (i.e., a total sample size of

Table 1 Demographic profile of patients.

Variables	Group D (n = 50)	Group F (n = 50)
Age (years)	33.02 (29.96–36.07)	30.82 (28.10–33.61)
Weight (kg)	54.24 (51.33–57.14)	56.2 (53.09–59.30)
Sex		
Male	13	21
Female	37	29
ASA		
I	25	34
II	25	16

Continuous variables presented as mean (95% CI).
ASA, American Society of Anesthesiologists.

98, assuming equal group sizes) to achieve a power of 90% and a level of significance of 5% (two-sided) to detect a true difference in means between the test and the control group of 10 units for heart rate. Finally, 50 patients were enrolled in each group.

All statistical analyses were performed using Stata version 10 (Stata Corp, Texas, USA). Continuous variables are presented as mean with 95% confidence interval, and the *t*-test was applied to compare the difference of means between two groups after checking the normal condition. Chi-square test was applied to test the independence of attributes of categorical variables. Power analysis was performed using software G*Power version 3.1.9.2 and for determining effective sample size on the basis of 10 units of heart rate difference between the two groups. Repeated measures two-way ANOVA was performed to compare the outcome variables between test and control groups, over the time and interaction between group and time. A *p*-value less than 0.05 was considered as statistical significance.

Results

One hundred patients were recruited for the study and there was no dropout (Fig. 1). Table 1 presents baseline demographic and clinical profiles of the patients in groups D and F. No significant difference was observed in any of the variables compared between both groups. Table 2 presents the comparison of heart rate of patients in groups D and F measured at various time points after drug intervention. Two-way ANOVA was performed to examine the change in heart rate after drug intervention between two groups and over time. There was significant interaction between groups and the time of measurement of heart rate (F[4,490] = 2.63, p = 0.0338). Simple main effects analysis showed that the heart rate changed significantly over time (p = 0.006), but overall, there was no significant difference in heart rate between the two groups (p = 0.066). The heart rate at the baseline was not significantly different between the two groups (p = 0.1579). However, heart rate of the patients in group D was significantly lower compared to Group F after 2 minutes (p = 0.0073); after that, there was no significant difference of the heart rate of patients in both groups.

Similarly, two-way ANOVA was performed to examine the change in heart rate of patients after intubation between the two groups and over the time. There was no significant interaction between the groups and time of measurement of heart rate after intubation (F[4,490] = 1.14, p-value = 0.338). No significant difference of heart rate after intubation was observed between the two groups at any point of time (p = 0.992)

Figure 2 presents the comparison of heart rate of patients in both groups measured at various points of time after intubation showing almost similar values. Table 3 presents the comparison of mean arterial pressure of patients in groups D and F measured at various points of time after drug intervention, and after intubation. Two-way ANOVA was performed to examine the change in mean arterial pressure after drug intervention between two groups and over the time. There was significant interaction between the groups and time of measurement of mean arterial pressure – F(4,490) = 2.59, p = 0.0362. Simple main effects analysis showed that the mean arterial pressure changed significantly over the time (p = 0.0001), and also between D and F groups (p = 0.0055). Mean arterial pressure at the baseline was not significantly different between the two groups (p = 0.9067). However, mean arterial pressure of the patients in group D was significantly lower as compared to Group F after 4 minutes (p = 0.0067) and 6 minutes (p = 0.0194).

Similarly, two-way ANOVA was performed to examine the change in mean arterial pressure of patients after intubation between the two groups and over the time. There was no significant interaction between the groups and time of measurement of mean arterial pressure after intubation – F(4,490) = 0.04, p-value = 0.9962. No significant difference of mean arterial pressure after intubation was observed between two groups at any point of time (p = 0.6743). Figure 3 presents the comparison of mean arterial pressure of patients in both groups measured at various points of time after intubation showing almost similar values.

Discussion

The main finding of this study was that dexmedetomidine 0.5 $\mu g.kg^{-1}$ was as effective as fentanyl 2 $\mu g.kg^{-1}$ in attenuating the hemodynamic response accompanying laryngoscopy and tracheal intubation.

Fentanyl, along with lidocaine, is supposed to be best suited for achieving the criteria for attenuation of stress response to laryngoscopy and intubation.[7] Fentanyl attenuates the response at 2 $\mu g.kg^{-1}$ administered 5 minutes before laryngoscopy and intubation.[11–13]

Various studies have concluded that dexmedetomidine attenuates the stress-induced sympathoadrenal responses to tracheal intubation. These studies used various dosage of dexmedetomidine infusion for this purpose.[4–6] The earliest study by Jaakola et al. concluded that dexmedetomidine attenuates the increase in heart rate and blood pressure during intubation following 0.6 $\mu g.kg^{-1}$ infusion, which is almost similar to the dose used by us but administered as a bolus.[14]

Later studies have focused on the effect of dexmedetomidine in attenuation of reflex response to tracheal extubation after general anesthesia also. Guler et al. concluded that a single-dose bolus injection of 0.5 $\mu g.kg^{-1}$ dexmedetomidine before tracheal extubation attenuates airway-circulatory reflexes during extubation as compared to placebo.[8] Similar findings were observed by Turan et al., who administered

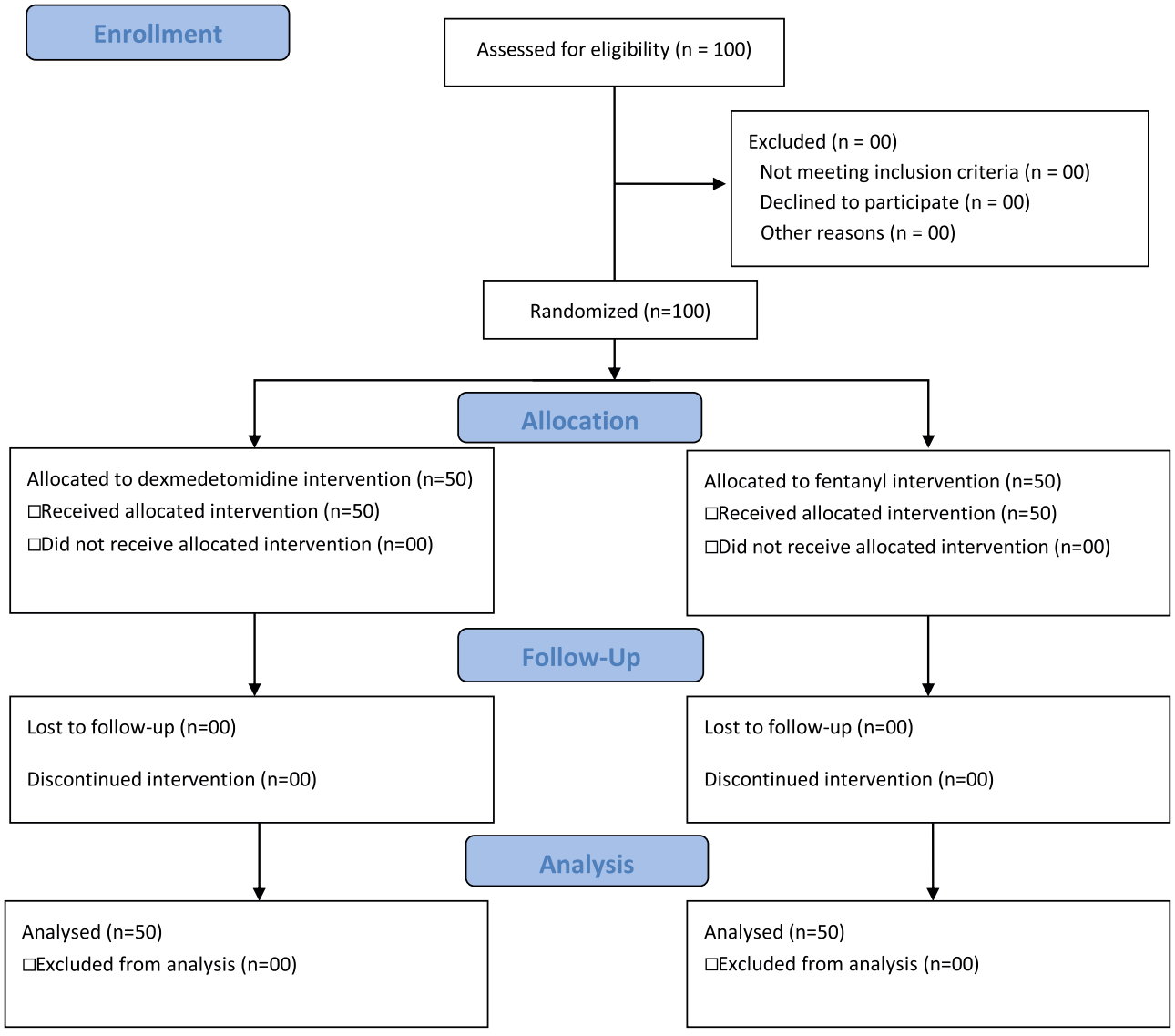

Figure 1 Consolidated Standards of Reporting Trials flow diagram of participants through the study.

Table 2 Comparison of heart rate (beats per minute) of patients in both groups after drug intervention and following intubation.

Time	After drug intervention		Time	After intubation	
	Group D (n = 50)	Group F (n = 50)		Group D (n = 50)	Group F (n = 50)
Baseline	98.98 (93.44–104.51)	93.06 (86.79–99.38)	1 min	100.74 (96.07–105.4)	103.64 (98.93–108.43)
2 min	85.38 (79.86–90.89)	96.74 (90.49–102.98)	2 min	114.9 (81.56–148.23)	99.58 (95.21–103.94
4 min	87.96 (82.63–93.28)	95.64 (89.39–101.88)	3 min	92.86 (88.97–96.74)	96.64 (91.91–101.36)
6 min	88.38 (82.41–94.34)	89.66 (83.86–95.45)	4 min	89.6 (85.54–93.65)	94.12 (88.82–99.42)
8 min	84.22 (78.41–90.03)	86.58 (81.60–91.55)	5 min	88.03 (84.04–92.11)	92.04 (86.51–97.57)

same dose of dexmedetomidine over 60 seconds, 5 minutes before extubation.[9]

The patients are still under the effect of anesthetic agents prior to extubation. Dexmedetomidine administration at this point of time achieved better hemodynamics without any adverse effect following tracheal extubation. Based on the safety and efficacy of this dose of dexmedetomidine during extubation, we postulated that it might be effective during laryngoscopy and intubation also.

Till date, there is only one study published that used a single bolus dose of 2 $\mu g.kg^{-1}$ dexemedetomidine to evaluate the stress response to both tracheal intubation and extubation during general anesthesia.[15] In a randomized, double-blind study, the patients were administered 2 $\mu g.kg^{-1}$

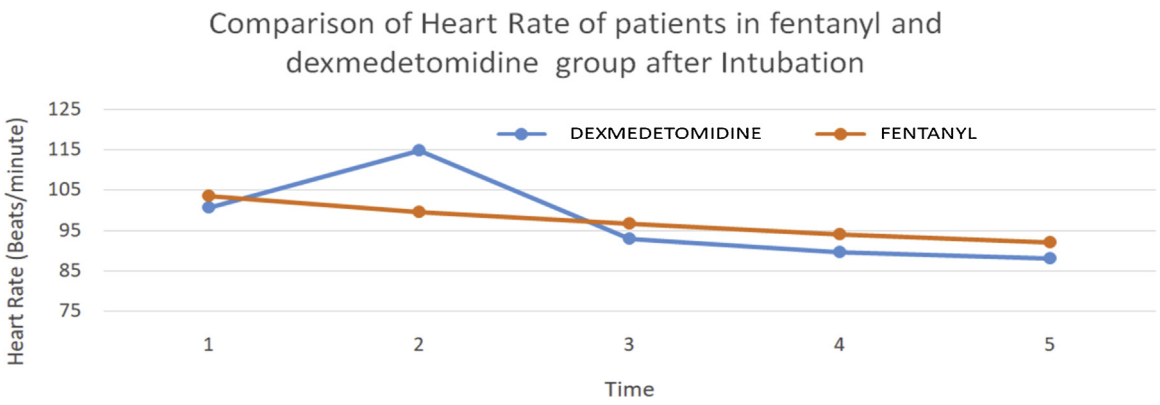

Figure 2 Comparison of heart rate of patients in both groups.

Table 3 Comparison of mean arterial pressure (mmHg) of patients in both groups after drug intervention and following intubation.

Time	After drug intervention		Time	After intubation	
	Group D (n = 50)	Group F (n = 50)		Group D (n = 50)	Group F (n = 50)
Baseline	96.44 (93.02–99.85)	96.7 (93.84–99.50)	1 min	101.84 (96.66–107.01)	100.82 (96.13–105.5)
2 min	91.52 (88.95–94.08)	92.34 (89.57–95.10)	2 min	94.28 (89.49–99.06)	93.2 (89.02–97.37)
4 min	83.52 (80.52–86.52)	90.84 (87.88–93.79)	3 min	85.9 (82.24–89.55)	85.12 (81.68–88.55)
6 min	75.16 (72.12–78.10)	81.16 (77.02–85.29)	4 min	79.6 (76.15–83.05)	79.66 (76.42–82.9)
8 min	68.56 (65.20–71.91)	68.1 (64.63–71.56)	5 min	77.44 (73.58–81.29)	77.60 (74.41–80.78)

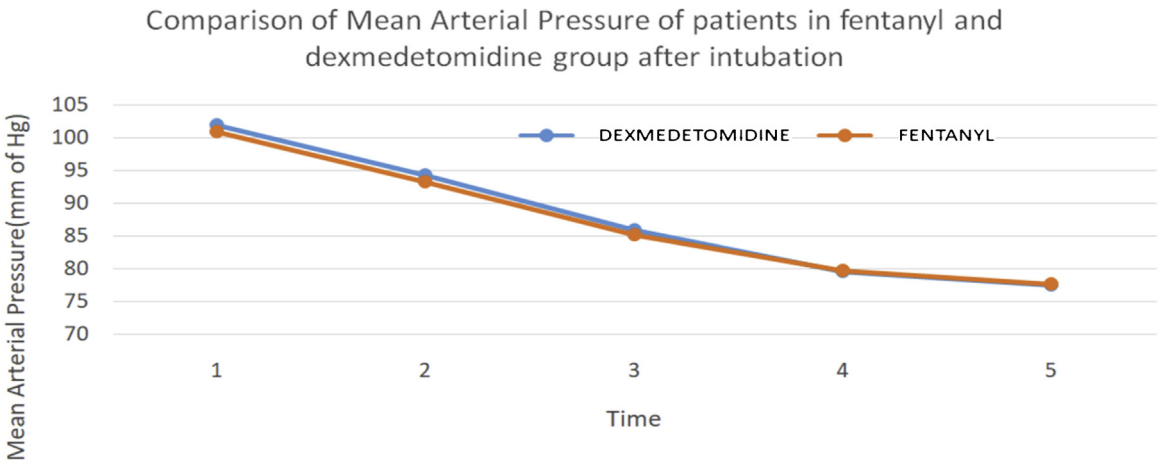

Figure 3 Comparison of mean arterial pressure of patients in both groups.

dexmedetomidine diluted in 20 mL saline that was administered over 5 minutes. The other group received saline injection. Anesthetic induction was performed 15 minutes later with fentanyl 2 $\mu g.kg^{-1}$ and thiopentone after 3 minutes of preoxygenation.

They observed that laryngoscopy and tracheal intubation resulted in significant increase in both heart rate and arterial pressure in the placebo group but not in the dexmedetomidine group.

There was some differences in the protocol adopted by them as compared to ours. They administered atropine 0.5 mg intramuscularly to all their patients 30 minutes before arrival in the operation room. We think this might have significantly affected the study findings. Apart from using a higher dose than ours, they administered it over 5 minutes and waited for another 15 minutes before induction. Despite atropine premedication, a few patients required it again for bradycardia. Ramsay sedation score of 4–5 was observed after 5 minutes, and 3 patients developed respiratory obstruction presumably secondary to excessive sedation. We believe that the dose and mode of dexmedetomidine administration in this study was not safe and useful.

Our study clearly showed a better profile of dexmedetomidine bolus that achieved its objective of obtunding the hemodynamic response to laryngoscopy and tracheal intubation that was accomplished in less time without any adverse

effect. There was no need for extra gadgets to provide infusion, and no need for extra monitoring of the patients during the busy operation room schedule.

The ideal anesthetic induction should not be time-consuming, should minimize the cardiovascular response, and should not influence the duration and modality of general anesthesia.[7] Hence, the dose and mode of administration used by us satisfies the objectives in a better way as compared to all other studies conducted with dexmedetomidine for attenuation of the hemodynamic response to laryngoscopy and intubation.

The hemodynamic effects of dexmedetomidine results from both peripheral and central mechanism.[3] There is a biphasic, dose-dependent effect on hemodynamics. At low doses, it causes a reduction in sympathetic tone that is mediated by a reduction of norepinephrine release at the neuroeffector junction. This causes an inhibition of neurotransmission in sympathetic nerves.[16] Ultimately, there is a significant reduction in circulating catecholamines, leading to a slight decrease in blood pressure and a modest reduction in heart rate.[17]

Fentanyl predominantly acts on μ opioid receptors. Fentanyl decreases sympathetic tone and increases parasympathetic tone via its action on cardiovascular and autonomic regulatory areas.

Dexmedetomidine has been used in doses ranging from 0.1 to 10 $\mu g.kg^{-1}.h^{-1}$, and there is a significant incidence of bradycardia and hypotension in higher doses.[18,19] In our study, the heart rate of the patients in dexmedetomidine group was significantly lower as compared to control after 2 minutes ($p = 0.0073$) of administration, but after that there was no significant difference of heart rate of patients in test and control groups. Mean arterial pressure of the patients in dexmedetomidine group was significantly lower as compared to that of fentanyl group after 4 minutes ($p = 0.0067$) and 6 minutes ($p = 0.0194$). We believe that the action of propofol might have contributed to this effect rather than dexmedetomidine alone.

Other studies have demonstrated a transient increase in heart rate and MAP initially during the administration of dexmedetomidine infusion, which is followed by a decrease in these values.[20,21] This is likely due to the vasoconstrictive effect of dexmedetomidine appearing earlier than the central sympathetic action.[22]

The hemodynamic changes did not require any intervention in the form of administration of atropine or mephentermine. We think the use of a smaller dose and waiting only 5 minutes before administering propofol might have been the reasons for these findings, which further substantiate the mode of dexmedetomidine usage in this study for achieving hemodynamic stability during laryngoscopy and intubation.

Our study had some important limitations. It was a single-center study, and the results may differ elsewhere. There was a critical limitation in terms of the relatively smaller number of ASA I–II patients only. A placebo group was not included due to ethical issues. Further, hemodynamic stability offered by the study medications would have been better established by measuring plasma catecholamine level. Also, alprazolam administration one night before the procedure might have some influence on the results. Further clinical studies are needed to resolve these problems.

Conclusion

Dexmedetomidine 0.5 $\mu g.kg^{-1}$ administered as a bolus is as effective as fentanyl in attenuating the hemodynamic response accompanying laryngoscopy and tracheal intubation without causing any hemodynamic adverse effect. It may be considered an alternative to opioids for this purpose.

Conflicts of interest

The authors declare no conflicts of interest.

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