Comparison of dexmedetomidine and clonidine for attenuation of sympathoadrenal responses and anesthetic requirements to laryngoscopy and endotracheal intubation

Shirsendu Mondal*, Hindol Mondal, Ritaban Sarkar, Musikur Rahaman

INTRODUCTION

Laryngoscopy and tracheal intubation are nearly always associated with an increase in the blood pressure and an increase in the heart rate (HR) due to the reflex sympathetic discharge which is caused by epipharyngeal and laryngopharyngeal stimulation. This increased sympathoadrenal activity may result in hypertension, tachycardia, and arrhythmias.1

Though these changes are well-tolerated by healthy individuals, they may be fatal in patients with hypertension, coronary artery disease, or intracranial hypertension. To “blunt” this pressor response, various pharmacological agents have been tried, which include β-adrenergic blockers, vasodilators, calcium channel blockers, intravenous (IV) opioids, and local anesthetics.2-5 α2-Adrenergic agonists decrease sympathetic tone and preoperative use of clonidine has been shown to blunt the hemodynamic responses to noxious stimulation and to prevent the overall hemodynamic variability. It has also sedative and anesthetic sparing effects.6-7 Dexmedetomidine is a highly selective α2 receptor agonist having 8 times high affinity and α2 selectivity compared to clonidine and has a shorter duration.

ABSTRACT

Background: Laryngoscopy and tracheal intubation after the induction of anesthesia are nearly always associated with a sympathetic hyperactivity. To attenuate the pressor response, various drugs have been tried, but studies to compare the effects of dexmedetomidine or clonidine on the hemodynamic response during laryngoscopy and tracheal intubation are anecdotal and sparse. This study aims to find the drug, which was best suited for this purpose and to compare their effects on sedation and anesthetic requirements.

Methods: This was a prospective study, which involved three groups of patients. Each group had 20 patients who presented for elective, non-cardiovascular surgeries. The patients in group I (control) were given normal saline and the groups II and III were given dexmedetomidine and clonidine, respectively. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and Ramsay sedation score were recorded at 1 and 2 min after completion of administration of study drug. Induction was done with propofol and required dose is noted. HR, SBP, and DBP were again assessed during intubation and at 1, 3, 5, and 10 min after intubation. The obtained clinical data were analyzed statistically with analysis of variance.

Results: In our study, HR, SBP, and DBP all increased during intubation and thereafter in all three groups. Pretreatment with dexmedetomidine 1 μg/kg and clonidine 2 μg/kg significantly attenuated the cardiovascular and catecholamine responses to tracheal intubation. However, attenuation was significantly more with the dexmedetomidine group with a quicker return to baseline. Dexmedetomidine also fared in terms of anesthetic requirement (propofol) and sedative action.

Conclusion: Preoperative administration of a single dose of dexmedetomidine blunted the hemodynamic responses more than clonidine or placebo during laryngoscopy, and reduced anesthetic requirements.

Keywords: Clonidine, Dexmedetomidine, Anesthetic requirement, Hemodynamic response
of action than clonidine. It provides anesthetic sparing effects, anxiolysis, “cooperative sedation” and analgesia without respiratory depression. The mechanism of action of dexmedetomidine differs from clonidine as it possesses selective α2-adrenoceptor agonism, especially for the 2A subtype of this receptor, which causes it to be a much more effective sedative and analgesic agent than clonidine.

This prospective, randomized, double-blinded study was planned to compare dexmedetomidine and clonidine for the attenuation of pressor response during laryngoscopy and intubation, effect on anesthetic requirements and effect on sedation.

METHODS

The study was approved by institutional Ethics Committee. The study population comprised of 60 patients of American Society of Anesthesiologists (ASA) grades 1 and 2, aged between 20 and 65 years, scheduled for major elective surgery. Written informed consent was taken from each patient. All the patients underwent a pre-anesthetic evaluation, which comprised of a detailed history taking, a clinical examination in either the anesthesia OPD or at the bed side and evaluation of the investigations. Pregnant and nursing woman, patient with morbid obesity, having underlying cardiovascular or other systemic disease, diabetes, taking any non-permitted medications or known allergic to study medications were excluded. The patients were randomly assigned to one of the three groups, each containing 20 patients, using Random Allocation Software version 1.0.0. Allocation concealment was ensured with sealed opaque envelope. The study was conducted in a double-blind fashion by the use of coded syringe. The patients in group I (control) were given normal saline (NS) and groups II and III were given IV dexmedetomidine and clonidine, respectively.

After the arrival of patients to the operating room, multichannel monitor (electrocardiogram, oxygen saturation, non-invasive blood pressure) was attached and monitored continuously. Preoxygenation with 100% oxygen was given for 5 min. All the patients received glycopyrrolate 0.2 mg IV, ondansetron 4 mg IV, and fentanyl 2 μg/kg IV as premedication.

Before the laryngoscopy, the patients in group I (control) were given NS (10 ml IV over 10 min). The patients in group II were given dexmedetomidine (1 μg/kg dissolved in 10 ml NS IV over 10 min), and group III were given clonidine (2 μg/kg dissolved in 10 ml of NS IV over 10 min).

The patients’ HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were recorded before drug administration (basal), at 1 min, 2 min following administration of study drugs. Ramsay sedation score was studied, and level of sedation was assessed at 1 and 2 min after administration of the drug. Then induction was done with propofol 1% and dose requirement for loss of verbal contact was noted. Intubation was facilitated with vecuronium 0.1 mg/kg IV. All the intubations were done by expert anesthesiologist within 15 s.

HR, SBP, and DBP were noted during intubation, then after 1, 3, 5 and 10 min after intubation.

The data at each of the measurement points was compared and analyzed using the analysis of variance (ANOVA).

RESULTS

All the groups were comparable in their age, gender, and body weight distribution. There was no significant intergroup difference from the baseline. ASA grade were similar and mean duration of surgery were also comparable in all groups and found to be statistically non-significant (p>0.05).

Heart rate

One-way ANOVA study showed significant variations in the control group compared to dexmedetomidine and clonidine groups in the HR before and after the endotracheal intubation and at time intervals of 1, 3, 5, and 10 min (p<0.0001).

At 1 and 2 min after administration of drug, dexmedetomidine group had decreased HR significantly than the control group (p<0.01), but not compared to clonidine (p>0.05).

The difference in the HR between the dexmedetomidine group and the other groups remained statistically significant during intubation, at 1 and 3 min of the assessment (p<0.05). At 5 and 10 min, though the difference in HR between dexmedetomidine group and control group was still significant (p<0.001), it was not significant in comparison to clonidine group (p>0.05) (Figure 1).

Systolic blood pressure

The changes in the SBP and their statistical comparisons indicates that though there was an increase in SBP in all
three groups, measured 1 min after drug administration, the difference was not significant. However, 2 min after drug administration both dexmedetomidine and clonidine group started to decrease SBP (attenuation is more with dexmedetomidine and the difference is significant, \( p<0.05 \)), whereas in the control group SBP remained elevated with a difference that is statistically significant compared to dexmedetomidine (\( p<0.01 \)), but not compared to clonidine (\( p>0.05 \)).

Statistically significant difference was observed with the dexmedetomidine and clonidine groups compared to the control group during intubation and the subsequent assessments at 1, 3, 5, and 10 min (\( p<0.001 \)).

The attenuation of the SBP was highly significant in the dexmedetomidine group as compared to that in the clonidine group (\( p<0.05 \) at intubation, 1 and 3 min and \( p<0.001 \) at 5 and 10 min). During the laryngoscopy and intubation, a maximum rise of only 7.14% (135.3 ± 15.19) was observed from its baseline (126.45 ± 15.05) as compared to the 14.67% (148.05 ± 10.01) increase in the clonidine group from its baseline (129.45 ± 11.02) (\( p<0.05 \)) and 25.56% (167.7 ± 15.97) increase in the control group from baseline (133.5 ± 17.38). At 10 min, the SBP, which was recorded was 4.76% (120.25 ± 7.88) lower than the basal value in dexmedetomidine group, which was nearly equal to baseline in clonidine group (129.45 ± 11.02) and 16.54% (155.4±5.85) more than the baseline value (133.5±17.38) in the control group (\( p<0.001 \)) (Figure 2).

**Diastolic blood pressure**

One-way ANOVA showed no significant difference in DBP among all the groups at 1 min after drug administration. However, 2 min after drug administration, dexmedetomidine group had a significant decrease in DBP compared to control (\( p<0.001 \)) and clonidine (\( p<0.05 \)) groups, though no significant difference in between control and clonidine group was observed.

A significant difference was observed from the control in both dexmedetomidine and clonidine group (\( p<0.001 \)) during intubation and at all the subsequent levels. The maximum rise was only 3.75% (83.05 ± 9.07) in dexmedetomidine group, statistically significant than 19.23% (93.45 ± 7.09) in clonidine group (\( p<0.001 \)) and 30.57% (100.8 ± 7.87) in the control group (\( p<0.001 \)) during intubation.

Dexmedetomidine was efficient in the attenuation of the DBP compared to clonidine at all the time intervals after intubation that is, at 1, 3, 5, and 10 min (\( p<0.05 \)). It achieved 5% (76 ± 8.18) lower values than the basal DBP value (79.95 ± 10.21) at 10 min compared to 3.84% (81.7 ± 6.05) higher than basal DBP value of clonidine (78.05 ± 9.32) and 27.27% (98.5 ± 3.08) higher than basal value of control (77.2 ± 9.48), which was statistically significant (\( p<0.05 \) and \( p<0.001 \), respectively) for clonidine and control group (Figure 3).

**Mean propofol dose**

Mean induction dose of propofol was significantly less in both dexmedetomidine (55 ± 6.88) and clonidine group (74 ± 8.2) compared to the control group (95 ± 9.46, \( p<0.001 \) in both). Difference between dexmedetomidine group and clonidine group was also significant statistically (\( p<0.001 \)) (Figure 4).

**Ramsay sedation score**

Ramsay sedation score was applied, and sedation level was studied. In dexmedetomidine group mean sedation score (2.5 ± 0.5 after 1 min, 2.55 ± 0.5 after 2 min of drug administration) was more as compared to clonidine group (2.05 ± 0.39 after 1 min, 1.95 ± 0.51 after 2 min of drug administration), which was statistically significant (\( p<0.05 \)) and both of these groups produced significantly more sedation than the control group (1.45 ± 0.51 after 1 min, 1.1 ± 0.31 after 2 min of drug administration, \( p<0.001 \)) (Figure 5).
DISCUSSION

The endotracheal intubation and laryngoscopy were associated with a rise in plasma catecholamine concentration and subsequent increase in the blood pressure, HR and the cardiac dysrhythmias. These above-mentioned effects may have serious repercussions on the high-risk patients like those with cardiovascular disease, increased intracranial pressure, or anomalies of the cerebral vessels. Attenuation of such responses is of great importance in the prevention of the perioperative morbidity and the mortality.\(^\text{11}\)

The hemodynamic response to laryngoscopy and endotracheal intubation has been a topic of discussion since 1940, when Reid and Brace\(^\text{12}\) found that the stimulation of the upper respiratory tract provoked an increase in the vagal activity. A year later, Burstein et al.\(^\text{13}\) totally contradicting Reid’s statement, found that the pressor response was due to an augmented sympathetic activity, which was provoked by the stimulation of the epipharynx and the laryngopharynx, which was further confirmed by Prys-Roberts.\(^\text{12}\)

A diversity of results exist about the protective measures against the hemodynamic and the catecholamine responses to laryngoscopy and intubation, but no single anesthetic technique has become generally accepted as being effective in preventing or attenuating these responses. Many techniques have been recommended. The drugs which were used were either partially effective or they produced other undesirable effects on the patients.\(^\text{14}\)

In any study which is conducted, the criteria for the selection of the appropriate drug to prevent a sympathetic response must include the following. The drug must be applicable, regardless of the patient collaboration, and it must prevent impairment of the cerebral blood flow and avoid the arousal of the patient. The administration of the drug should neither be time consuming nor should it affect the duration or the modality of the ensuing anesthesia. Intravenous dexmedetomidine and clonidine appear to best fulfill the above criteria.\(^\text{15}\)

The \(\alpha_2\)-adrenoceptor agonists have been used as premedicants because of their beneficial properties in anesthesia. Clonidine, which is mainly used as an anti-hypertensive agent, has many properties of an ideal premedicant, and it also has beneficial effects on the hemodynamics during stressful conditions like laryngoscopy and endotracheal intubation.\(^\text{16}\) The effects of clonidine on the hemodynamic variables are dose related, but they increase the dose to more than 4 \(\mu g/\text{kg}\) and do not further enhance the efficacy. Hence, in this study, we used 2 \(\mu g/kg\).

Dexmedetomidine is a highly selective \(\alpha_2\) receptor agonist having eight times high affinity and \(\alpha_2\) selectivity compared to clonidine and has a shorter duration of action than clonidine.\(^\text{8,9}\) With dexmedetomidine use, there is a significant reduction in circulating catecholamines with a decrease in blood pressure and a modest reduction in HR.\(^\text{17,18}\) Sağiroğlu et al.\(^\text{19}\) conducted a study with different doses of dexmedetomidine and found that to control hemodynamic responses to tracheal intubation, dexmedetomidine 1 mcg/kg is more effective than dexmedetomidine 0.5 \(\mu g/kg\) without any side-effect. Hence, we conducted the study with a dose of 1 \(\mu g/kg\) of dexmedetomidine.

This study was undertaken to compare the effects of dexmedetomidine and clonidine on the attenuation of the hemodynamic response to laryngoscopy and endotracheal intubation. This study also tried to find out the effect of these two drugs on peri-operative sedation and changes in anesthetic dose required for induction.

In this study, pretreatment with \(\alpha_2\)-adrenergic agonist dexmedetomidine 1 \(\mu g/kg\) attenuated, but did not totally abolish the cardiovascular and catecholamine surge responses to laryngoscopy and tracheal intubation after induction of anesthesia.

After administration of dexmedetomidine and clonidine before intubation there was a fall in mean HR compared to control group, which was statistically significant in case of dexmedetomidine at 1 and 2 min (\(p<0.01\) and 0.001,
respectively) and clonidine at 2 min (p<0.001), but not statistically significant in clonidine at 1 min (p>0.05). Keniya et al.20 also observed bradycardia in their study with dexmedetomidine. Both SBP and DBP increased after 1 min of drug administration, but the difference was not significant. Similar increase in blood pressure was observed by Bloor et al.21 At 2 min dexmedetomidine started to decrease in blood pressure and the difference was now significant compared to clonidine and control group (p<0.05).

During laryngoscopy and intubation and immediately after it, the rise in the HR and the blood pressure was maximum in all the groups. This finding was in agreement with those of the studies which were done by Smith and Derbyshire et al.,22 and Shribman et al.,23 who concluded that the plasma catecholamine concentration increased to the maximum within 1 min after the laryngoscopy. The rise was statistically highly significant within each group.

However, the dexmedetomidine group showed better attenuation of the HR as compared to the other two groups, which was statistically highly significant (p<0.001) up to 3 min of observation. Thereafter, the HR attenuation effect becomes comparable between dexmedetomidine and clonidine, but both remained significantly better than the control group.

The SBP and DBP increased after intubation compared to baseline, but an increase is significantly less with dexmedetomidine compared to clonidine and control group (p<0.05) at all levels of assessments. During laryngoscopy and intubation, the maximum rise of only 7.14% was observed in dexmedetomidine from its baseline as compared to 14.67% increase in the clonidine group from its baseline (p<0.05) and 25.56% increase in the control group from baseline (p<0.001).

In the dexmedetomidine group pressure came to baseline or below baseline at 3 min of intubation. In the clonidine group, this return of blood pressure towards baseline occurred gradually over 10 min, whereas the increased blood pressure was maintained even at 10 min in the control group.

Scheinin et al.17 also observed that dexmedetomidine attenuated the cardiovascular responses to laryngoscopy and tracheal intubation. In their study, they measured catecholamine concentration and found that the concentration of noradrenaline in mixed venous plasma was smaller in the dexmedetomidine group during all phases of induction.

The hemodynamic effects of dexmedetomidine probably resulted from peripheral and central mechanism. α2-Adrenoreceptor agonists show a biphasic, dose-dependent, blood pressure effect. At low doses, the dominant action of α2-adrenoreceptor agonist activation is a reduction in sympathetic tone, mediated by a reduction of norepinephrine release at the neuroeffector junction, and an inhibition of neurotransmission in sympathetic nerves.21 The net effect of dexmedetomidine action is a significant reduction in circulating catecholamines with a slight decrease in blood pressure and a modest reduction in HR.18

In our study, we observed that requirement of propofol was significantly (p<0.001) less in dexmedetomidine group than in the clonidine group as was found by Scheinin et al. regarding the requirement of thiopentone.17

Sedation was significantly more in dexmedetomidine group at 1 min and 2 min after infusion of the drug, but SpO2 was not affected. Sağoğlu et al.19 also found no respiratory depression or decrease in SpO2 with similar dose of dexmedetomidine. In another study, in which the infusion of opioid and α2-adrenergic agonists were compared, it was concluded that dexmedetomidine does not cause significant respiratory depression and it decreases the risk of apnea.24

Many other authors have used single dose dexmedetomidine prior to induction and have achieved suppression of hemodynamic responses during laryngoscopy and intubation and also have noticed the reduction of anesthetic requirement.17,19 Stress response to extubation is equally suppressed by dexmedetomidine given prior to reversal.25,26

CONCLUSIONS

Based on the present clinical comparative study, the following conclusions can be made:

- In patients, with no drugs to attenuate the sympathetic response to laryngoscopy and intubation, the maximum increases in the HR and the SBPs and DBPs were significantly high as compared to the pre-induction values.
- Dexmedetomidine significantly attenuated the sympathetic response to laryngoscopy and intubation.
- Clonidine also reduced the pressor response, but its effect was far lower than that of dexmedetomidine in attenuating the response.
- This study showed that dexmedetomidine was superior to clonidine in the attenuation of the pressor response and dexmedetomidine is also helpful providing sedation and decreasing requirement in anesthetic agent for induction.
- An intravenous dose of dexmedetomidine 1 μg/kg, which is administered before a laryngoscopy and an intubation can be recommended to attenuate the sympathetic response to the laryngoscopy and intubation without any side-effects of the drug.

There were some limitations of our study. Being unincentric in nature it was not feasible to validate our conclusion as the sample size was small (n=20 in each group). Though we found that propofol requirement was much less in the dexmedetomidine group, but depth of anesthesia was not substantiated by bispectral index monitoring. Measuring plasma catecholamine level would have established

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hemodynamic stability offered by dexmedetomidine more firmly. Further study with larger sample and hard endpoints would solidify the evidences accumulated from this study.

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