Original Research Article

Intravenous dexmedetomidine versus fentanyl to attenuate haemodynamic stress response to laryngoscopy and endotracheal intubation

V Y Srinivas¹, Priya K¹, Kokila N¹,*

¹ Dept. of Anaesthesiology, Mysore Medical College and Research Institute, Mysuru, Mysuru, Karnataka, India

A B S T R A C T

Background and Objective: Laryngoscopy and endotracheal intubation employed for general anaesthesia cause noxious stimuli and are associated with laryngo- sympathetic stimulation manifested by hypertension, tachycardia and arrhythmias. This study compares the efficacy of dexmedetomidine and fentanyl in attenuating haemodynamic stress responses to laryngoscopic endo-tracheal intubation in adult patients undergoing surgeries under general anaesthesia.

Materials and Methods: 90 adult participants of any sex aged between 18-55yrs undergoing elective surgeries under general endo-tracheal anaesthesia were divided into 3 groups of 30 patients in each group. Group C: Control group – received 10ml of normal saline (NS) intravenously (IV) over 10 minutes (min), 10min before induction. Group D: Dexmedetomidine group - received IV Dexmedetomidine 0.6 mg/kg body weight diluted to 10ml of NS IV over 10min using a syringe pump and 3ml of NS IV 2min before induction. Group F: Fentanyl group - received 10ml of NS IV over 10min using a syringe pump and IV Fentanyl 2mg/kg body weight diluted to 3ml of NS IV 2min before induction. Anaesthesia was induced with IV Thiopentone sodium 5 mg/kg body weight and IV Vecuronium 0.1mg/kg body weight to facilitate endotracheal intubation. Lignocaine 1.5mg/kg IV was given 90seconds before intubation in all the groups. Anaesthesia was maintained with Oxygen, Nitrous Oxide, 1-2% Sevoflourane and IV Vecuronium. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded at various time intervals.

Results: In group C, 1min after laryngoscopy and intubation, the rise in HR, SBP, DBP and MAP were 42bpm, 30mmHg, 22 mmHg and 24mmHg respectively compared to basal values. In group F, 1min after laryngoscopy and intubation, the rise in HR was 14bpm, rise in SBP, DBP and MAP each by 2mmHg compared to basal values. In group D, HR, SBP, DBP and MAP were decreased by 4bpm, 23 mmHg, 25mmHg and 24 mmHg respectively compared to basal values at 1min after laryngoscopy and intubation which was statistically highly significant (p=0.000).

Interpretation and Conclusion: Both IV Dexmedetomdine 0.6μg/kg body weight administered over 10min and IV Fentanyl 2μg/kg body weight administered over 2min prior to induction are effective in obtunding the haemodynamic stress response to laryngoscopy and intubation without any significant side effects. However IV Dexmedetomidine is more effective and superior than Fentanyl in attenuating haemodynamic response to laryngoscopy and endotracheal intubation.

© 2019 Published by Innovative Publication. This is an open access article under the CC BY-NC-ND license (https://creativecommons.org/licenses/by/4.0/)

1. Introduction

Laryngoscopy and endotracheal intubation are the most important and essential skills to be mastered by an anaesthesiologist. Intubation provides a safe secured airway, can be used to administer anaesthetic gases and also it minimizes the risk of aspiration. But the procedure is commonly accompanied by increase in arterial blood pressure (BP) and heart rate (HR). The mechanism of hypertension and tachycardia is due to the sympathetic response with increased activity of catecholamines. The responses stay for a short duration
and are better tolerated by normal healthy individuals. But in patients with cardiovascular diseases like hypertension, ischemic heart disease, cerebrovascular disease with raised intracranial pressure, intracranial aneurysms, even these transient hemodynamic changes can result in potentially harmful effects like myocardial ischemia, left ventricular failure, pulmonary edema, ventricular dysrhythmias, stroke and cerebral haemorrhage.\(^2\) So prior to laryngoscopy, additional pharmacological measures like use of topical and intravenous lidocaine, volatile anaesthetics, opioids, vasodilators like Sodium nitroprusside and Nitroglycerine, Calcium channel blockers and \(\beta\)-blockers have been tried to obtund the sympathetic response.\(^5\) Recently, alpha-2 agonists like Clonidine and Dexmedetomidine have been tried for attenuating sympathetic stress response.\(^15\)

Both Clonidine and Dexmedetomidine binds to both \(\alpha-1\) and \(\alpha-2\) adrenergic receptors. Dexmedetomidine is highly specific and selective for \(\alpha-2\) receptor with \(\alpha 2: \alpha 1\) binding selectivity ratio of 1620:1 when compared to Clonidine whose binding ratio is 220:1. Dexmedetomidine, a centrally acting \(\alpha-2\) agonist has shown to be effective in blunting the haemodynamic stress response to laryngoscopy and tracheal intubation.\(^16\)–\(^18\) Fentanyl, one of the potent opioid analgesic used during general anaesthesia also shown to attenuate haemodynamic stress response to intubation.\(^16\)–\(^18\) Since both Fentanyl as well as Dexmedetomidine can suppress the sympathetic response to laryngoscopy and endo-tracheal intubation, a study was required in order to know which is more efficacious among them. Hence, the present study was undertaken to compare the effectiveness of Dexmedetomidine (0.6\(\mu\)g/kg), an alpha 2 adrenergic receptor agonist with Fentanyl (2\(\mu\)g/kg), a \(\mu\)-opioid receptor agonist in attenuation of the haemodynamic stress response to laryngoscopy and endotracheal intubation. Side effects like hypotension, bradycardia, sedation, nausea, vomiting and others were also being studied.

2. Materials and Methods

After obtaining institutional ethical committee clearance, this prospective study was conducted on 90 adult patients belonging to grade 1 and 2 of American Society of Anaesthesiologists (ASA) physical status, aged between 18-55 yrs. posted for surgeries under general anaesthesia. The study participants were randomly divided into 3 groups with 30 subjects in each group using shuffled opaque sealed envelopes in which the group name was written and then the subject was asked to pick the envelope. A senior anaesthesiologist who was not involved with the follow up study will open the picked envelope and prepares the test drug. After routine pre-anaesthetic check-up, a valid written informed consent was obtained from all the participants and all of them were kept nil per oral since midnight. Patients with cardiac, renal, hepatic, cerebral diseases and peripheral vascular diseases, hypertension, patients with heart HR less than 60 bpm, systolic BP less than 100 mmHg, heartblock, difficult airway, thyroid disorders and diabetes mellitus were excluded from the study.

In the operation theatre, preoperative baseline parameters such as HR, SBP, DBP and MAP were recorded using a multipara monitor. Intravenous access using 18G cannula was established and ringer lactate fluid was started followed by administration of study drugs.

Group C: Control group - received 10ml of NS IV over 10min using a syringe pump. 3ml of NS was administered IV 2min before induction.

Group D: Dexmedetomidine group - received IV Dexmedetomidine 0.6\(\mu\)g/kg body weight diluted to 10ml of NS IV over 10min using a syringe pump. 3ml of NS was administered after 8min IV 2min before induction.

Group F: Fentanyl group - received 10ml of NS IV over 10min using a syringe pump and IV Fentanyl 2\(\mu\)g/kg body weight diluted to 3ml of NS was administered IV 2min before induction.

All the subjects were premedicated with IV Midazolam 0.02mg/kg body weight after test drug administration. The subjects were preoxygenated for 3min with 100% oxygen. Anaesthesia was induced with IV Thiopentone sodium 5mg/kg body weight and endotracheal intubation was facilitated with 0.1mg/kg body weight IV Vecuronium. All the subjects were administered with 1.5mg/kg body weight of IV Lidocaine 90 seconds before intubation. After ventilating the subject with 100% Oxygen and 2% Sevoflurane for 3 minutes, laryngoscopy was performed with Macintosh laryngoscope blade and high volume low pressureuffed endotracheal tube was inserted into the trachea. After confirmation of bilateral equal air entry, the endo-tracheal tube cuff was inflated, tube fixed and connected to closed circuit. Anaesthesia was maintained with 50% nitrous oxide, 50% oxygen and 1 -2% sevoflurane by intermittent positive pressure ventilation and intermittent doses of IV vecuronium at 0.01mg/kg to facilitate muscle relaxation. At the end of the surgery, neuromuscular blockade was reversed with IV Neostigmine 0.05mg/kg and IV Glycopyrrolate 0.01 mg/kg.

Intraoperatively HR, SBP, DBP, MAP were recorded at the following time intervals: baseline, 2, 5, 8 minutes after study drug, before and after induction and then at 1, 3, 5, 10 minutes after laryngoscopy and intubation.

2.1. Statistical methods

The sample size was decided in consultation with the statistician and was based on initial pilot study observations, indicating that approximately 23 patients should be included in each group in order to ensure a power of 0.80 for detecting clinically meaningful difference by 15% in heart rate and mean arterial blood pressure. Assuming a 5% drop out rate, the final sample size was set at 30 patients in each group, which would permit a type 1 alpha error of 0.05
and type 2 beta error of 0.2. The results obtained in the study were presented in a tabulated manner and analysed using Microsoft Excel and SPSS 20 software. The results of the present study between the three groups was compared statistically using Analysis Of Variance (ANOVA), Student ‘t’ test and independent samples ‘t’ test. A ‘p’ value of < 0.05 was considered statistically significant and less <0.01 was considered as highly significant.

3. Results

All the three groups were comparable with regard to mean age, sex, weight, duration of laryngoscopy and surgery.

The basal HR was comparable among all the three groups and was statistically not significant (p=0.84). There was a statistically highly significant fall in HR after 2nd minute of drug infusion in group D compared to group F and group C. In group C, there was an increase in HR at 1st minute after laryngoscopy and intubation by 42bpm compared to the basal value, which did not return to the basal value even at 10th minute and in group F, there was an increase of 14 bpm as compared to basal value which returned to basal value by 10th minute, whereas in group D there was a decrease in HR by 4bpm as compared to the basal 1min after laryngoscopy and intubation. A statistically significant fall in mean HR was observed in Group D at all the time intervals till 10 minutes post-intubation compared to Group F (p=0.00) as shown in (Graph 1).

Graph 1: Mean heart rate comparison among all the groups

There was no statistically significant difference regarding the mean DBP among group C, group F and group D at basal and 2nd minute after drug infusion. There was statistically highly significant fall in DBP at 5th and 8th minute after study drug infusion, before induction, after induction and at 1st, 3rd, 5th and 10th minute after laryngoscopy and intubation in group F and group D as compared to group C. At 1st minute after laryngoscopy and intubation, there is an increase in mean DBP by 22mmHg in group C which reached the basal value by 10th minute and in Group F, at 1st minute there is an insignificant increase in mean DBP by 2mmHg above the basal value and reached the basal value by 3rd minute, whereas with group D, there is a decrease of DBP by 25mmHg at 1st minute after laryngoscopy and intubation compared to the basal value and remained below the basal value at all the time intervals which was highly significant (p=0.00). There was statistically highly significant (p=0.00) fall in mean DBP after 5th minute of study drug infusion till 10th minute after intubation in Group D compared to Group F as shown in (Graph 3).

Graph 3: Mean DBP comparison among all the groups

There was no statistically significant difference regarding the MAP among the three groups at basal and 2nd minute...
after drug infusion. There was statistically highly significant fall in MAP at 5th and 8th minute after study drug infusion, before induction, after induction and after laryngoscopy and intubation at 1st, 3rd, 5th and 10th minute in group F and group D as compared to group C. At 1st minute after laryngoscopy and intubation, there was an increase in MAP of 24mm Hg in group C which reached the basal value by 10th minute and in group F, at 1st minute there was an insignificant increase in MAP by 2mm Hg above the basal value which reached the basal value by 3rd minute whereas with Group D, there was a decrease of MAP by 23mmHg compared to the basal at 1st minute after laryngoscopy and intubation and remained below the basal value at all the time intervals following laryngoscopy and intubation which was highly significant (p=0.00) as shown in (Graph 4).

Graph 4: Mean MAP comparison among all the groups

4. Discussion

The most critical and invasive stimulus during administration of general anaesthesia is direct laryngoscopic endotracheal intubation. During the procedure, stimulation of laryngeal and tracheal tissues will activate the nociceptive receptors thereby activating sympathetic and adrenal response with release of catecholamines at nerve endings. The response is manifested as hypertension, tachycardia, laryngospasm, bronchospasm, increased intraocular and intracranial pressures and the effect peaks at 1min after intubation and return to baseline by 5-10min.1,3 The sympathetic response leading to haemodynamic changes depends on various factors like depth of anaesthesia, anaesthetic agent used, duration of laryngoscopy and intubation and also patient related factors. Various different pharmacological agents by different means have been adopted in various studies to obtund these haemodynamic stress responses to laryngoscopic intubation. But all such drugs and methods have their own limitations. Use of halothane was associated with dysrhythmias, calcium channel blockers produced reflex tachycardia, direct acting vasodilators needed invasive hemodynamic monitoring and lidocaine did not give consistent results, beta blockers blunt the HR response better than BP response.7,13,19–21

Recently α-2 agonists like Clonidine and Dexmedetomidine are being increasingly used to suppress the stress response as they showed a better effect than the commonly used drugs.15 Alpha 2 agonists act both on presynaptic and postsynaptically located α-2A receptors present in locus ceruleus within the brain. Presynaptic activation of α-2A receptors inhibits the release of noradrenaline causing hypnosis and sedation. So when these drugs are used along with other inhalational and intravenous anaesthetics decreased the requirement of these anaesthetics and analgesics. Postsynaptic activation of α-2A receptors in the brain decreases the sympathetic discharge leading to decrease in the HR and BP. Now a day, they are also becoming more popular for conscious sedation at low but at appropriate doses for procedures done outside the operation theatre without the risk of respiratory depression or PONV.

Dexmedetomidine hydrochloride is amindazolide compound with molecular weight of 236.7 and its empirical formula is C13H16N2HCl. It is the dextro- enantiomer of Medetomidine, the methylated derivative of Etomidine. Its specificity for the alpha-2 receptor is 8 times that of Clonidine. It has sedative, hypnotic, amnesic and analgesic properties and these effects are dose dependent. Its alpha 2 actions are short lived with elimination half time of 2 hours. Its action can also be reversed by the administration of a selective alpha-2 antagonist such as Atipamezole.22 So it is considered to be superior to Clonidine and is gaining popularity among the anaesthesiologists in the present day to day practice.

Various authors have used varying doses of Dexmedetomidine ranging from 0.5 μg/kg to 2μg/kg IV. Higher doses of 1-2μg/kg showed a better attenuation of hemodynamic response to laryngoscopy and intubation than 0.5μg/kg but are associated with more incidences of cardiovascular compromise like bradycardia and hypotension and also caused increased sedation. So in our study, we have used 0.6 μg/kg IV as used in other studies by Jaakola et al, Gandhi et al and Natta et al.16,23,24 Rapid bolus administration of Dexmedetomidine causes a transient increase in blood pressure with reflex decrease in heart rate due to activation of vascular smooth muscle α2 receptors located in the peripheral vasculature. We have diluted Dexmedetomidine with NS and infused slowly over 10min using syringe pump so that its peripheral actions are minimal. The distribution half time of Dexmedetomidine is around 6min. So after 10min of slow infusion of the drug, its action is adequate to suppress the CNS sympathetic activity during the procedure of direct laryngoscopic intubation.

Fentanyl, a synthetic, lipophilic, phenylpiperidine opioid agonist is popularly used as an IV analgesic. It is commonly used as a component of inhalational anaesthesia, balanced anaesthesia and neurolept analgesia and also used as a sole anaesthetic. It is 100 times more potent than morphine.
as an analgesic. 100μg of fentanyl cause analgesia similar to 10mg of morphine. It predominantly acts on μ receptors causing analgesia. Its actions can be reversed by Naloxone which is a selective μ receptor antagonists and its use has been approved by the FDA in suspected or proved cases of opioid overdosage. It has hemodynamic stabilizing property during perioperative period by its action on cardiovascular and autonomic regulatory areas. Fentanyl inhibits pituitary adrenal response directly or indirectly acting via hypothalamus. It attenuates the sympathoadrenal response at 2μg/kg IV given before laryngoscopy and intubation.\textsuperscript{5–7,16,18,21,24} Fentanyl at higher doses of 5-6μg/kg suppresses stress response better than the regularly used dose of 1-2μg/kg but higher dose may be associated with respiratory depression and delayed post operative recovery. In our study, we have given IV Fentanyl 2min before induction as its onset of action is 1-2min and by 5min when we do laryngoscopy and intubation, drug has reached its peak effect.

In our study, Dexmedetomidine group showed better attenuation of HR response compared to Control and Fentanyl groups. The HR remained below the basal value at all the time intervals after laryngoscopic intubation which was statistically highly significant (p=0.000). In Fentanyl group, HR returned to basal value only after 10min post -intubation. This is in conjunction with the studies done by Scheinin et al, Jaakola et al, Natta et al, Menda et al, Keniya et al, Gandhi et al, Das et al and Gunalan et al.\textsuperscript{16–18,23,24,26–28}

The attenuation of the rise in the SBP was highly significant in the Dexmedetomidine group as compared to that in the Control and Fentanyl groups. The SBP decreased and remained below the baseline value at all the time intervals in Dexmedetomidine group whereas there was a little rise in SBP during intubation in Fentanyl group and returned to basal value by 3min. Our study results correlated with the studies done by Scheinin et al, Jaakola et al, Natta et al, Menda et al, Keniya et al, Gandhi et al, Das et al, Gunalan et al, Kunisawa et al and Basar et al.\textsuperscript{16–18,23,24,26–30}

The attenuation of the rise in the DBP was highly significant in the Dexmedetomidine group as compared to that in the Control and Fentanyl groups. The DBP is significantly decreased in Dexmedetomidine group and remained below the baseline value at all the time intervals whereas there is insignificant fall of DBP in Fentanyl group. The same results were reported in the studies done by Scheinin et al, Jaakola et al, Natta et al, Menda et al, Keniya et al, Gandhi et al, Das et al, Gunalan et al, Kunisawa et al and Basar et al.\textsuperscript{16–18,23,24,26–30}

Both Dexmedetomidine and Fentanyl groups showed attenuation of the rise in the MAP and was significant as compared to that in the Control group. The decrease in MAP was highly significant in Dexmedetomidine group. Fentanyl group showed insignificant increase in MAP after 1min of intubation but then fell below the baseline after 3min. Our study results correlated with studies conducted by Scheinin et al, Jaakola et al, Natta et al, Menda et al, Keniya et al, Gandhi et al, Das et al, Gunalan et al, Kunisawa et al and Basar et al.\textsuperscript{16–18,23,24,26–30}

Studies by Jaakola et al and Mowfi et al had shown that Dexmedetomedine given before induction of anaesthesia decreased the intraocular pressure, HR and BP after intubation in patients undergoing ophthalmic surgeries.\textsuperscript{23,31} Jaakola et al also measured the plasma catecholamine levels and they noted the decrease d levels after Dexmedetomidine infusion and didn’t rise even after intubation.\textsuperscript{23} In our study, we have not measured the plasma catecholamine levels and the changes in intraocular pressure.

No cardiovascular side effects like hypotension and bradycardia were noted after the study drugs. Dexmedetomidine at a dose of 0.6 μg/kg when given slowly over 10 minutes didn’t cause hypertension/hypotension and bradycardia. Fentanyl didn’t cause much change in HR and BP as compared to Dexmedetomidine and so is considered to be a cardio-stable drug and preferred in patients with cardiovascular diseases. Nausea and vomiting were not seen with any of the study drugs till the induction of anaesthesia.

We have conducted the study on healthy ASA grade 1 and 2 patients. So, further studies are needed to be conducted on ASA grade 3 and 4 patients to know the efficacy of the study drugs on these high risk patients.

5. Conclusion
Our study demonstrates that intravenous single dose of Dexmedetomedine 0.6μg/kg body weight infused over 10 minutes and Fentanyl 2μg/kg body weight administered over 2 minutes prior to induction are effective in obtunding the hemodynamic stress response to laryngoscopic endotracheal intubation without any significant side effects. However IV Dexmedetomidine is more effective and superior than Fentanyl in attenuation of haemodynamic stress response to laryngoscopic endo-tracheal intubation.

6. Source of Funding
None.

7. Conflict of Interest
None.

References
3. Prys-Roberts C, Green LT, Meloche R, Foex P. Studies of anaesthesia in relation to hypertension II. Haemodynamic consequences of...
intravenous lignocaine.

J Clin Diagn Res
Fentanyl for stress attenuation during laryngoscopy and endotracheal intubation.
Comparative Study of Fentanyl and Dexmedetomidine in Attenuating
tracheal intubation.
Anesth Analg
coronary artery bypass graft patients.
J Clin Anesth
corrected

Author biography

V Y Srinivas Professor
Priya K Resident
Kokila N Assistant Professor