Efficacy of dexmedetomidine in attenuating pressor response during general anaesthesia- A randomised controlled trial

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Abstract

Introduction: Dexmedetomidine has shown promising results in obtunding pressor response during direct laryngoscopy and intubation. In this study we have investigated the efficacy of Dexmedetomidine in attenuating pressor response during intubation in terms of variation in mean arterial pressure (MAP), heart rate (HR) in patients undergoing elective surgery under general anaesthesia.

Materials and Methods: Subjects aged 20-50 years requiring general anaesthesia were allocated into group D (with Dexmedetomidine) and group P (without Dexmedetomidine) according to computer generated randomization table. After having met inclusion and exclusion criteria, obtained informed consent, patients were intubated orally with appropriate sized endotracheal tube (ETT) using direct laryngoscopy (DL) and intubation. End points were variation in MAP and HR at 0 minute and 5 minute of DL and intubation. Also other parameters like spo2 and EtCO2 were recorded.

Results: we found that there was highly significant statistical difference between group D and group P.

Conclusion: This comparative study of efficacy of Dexmedetomidine in attenuating pressor response has shown that it is very good premedication for controlling hypertensive episodes during direct laryngoscopy and intubation and thereby decreasing their untoward end organ effects on central nervous system and cardiovascular system.

Introduction

The pressor response to laryngoscopy and endotracheal intubation in the form of tachycardia, hypertension and arrhythmias, though transient, may be potentially dangerous. This response is due to reflex sympathetic discharge caused by pharyngeal stimulation. Transient hypertension and tachycardia are of major concern in those patients with ischemic heart disease or cerebrovascular accidents. These changes are the maximal at 1 minute after intubation and last for 5-10 minutes. Other drugs used routinely to alleviate intubation response have their own limitations.

The term premedication was 1st used in USA during 1920. Aims of premedication are anxiolysis, analgesia and reduction of premedication and thereby studying the efficacy of newer a2 agonist i.e., Dexmedetomidine. Specific a2 receptor agonism mediate sedation, hypnosis, analgesia, sympatholysis, neuroprotection. a2 receptors are found in CNS in highest densities in the Locus Ceruleus, predominant noradrenergic nuclei of brainstem. Pre-synaptic activation of a2A adrenoceptor in Locus ceruleus inhibits the nor-epinephrine (NE) release and results in decrease in sympathetic activity leading to hypotension and bradycardia.

a2 agonists like clonidine has been used in past for attenuation of sympatho-adrenal stimulation caused by tracheal intubation and surgery. Dexmedetomidine is new a2 agonist having eight times more affinity for a2 adrenoceptor as compared with Clonidine (has slow partial agonist activity)

Dexmedetomidine hydrochloride, an imidazole compound is the pharmacologically active s-enantiomer of medetomidine.

It is described chemically as (+)-4-(s)[2 3–(dimethylphenyl) ethyl]11 imidazole monohydrochloride and its specificity for the alpha-2 receptor is 8 times that of clonidine, with an alpha-2 : alpha-1 binding affinity ratio of 1620:1.

Preservative free dexmedetomidine is available in 1 ml ampoule as Dexmedetomidine Hydrochloride for intravenous use (Dexem, Themis Medicare Ltd., 100 µg/ml).

Specific alpha-2 receptor subtypes mediate the varied pharmacodynamics effects of Dexmedetomidine. Agonism at alpha 2A receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection and inhibition of insulin secretion. At the spinal cord, stimulation of alpha-2 receptors at the substantia gelatinosa of the dorsal horn leads

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Materials and Methods

After having obtained informed consent and ethical committee clearance one hundred patients (n=100) belonging to ASA (American Society of Anaesthesiologists) grade 1 and 2, aged 20-50 years posted for elective surgery under general anaesthesia were randomly allocated into group ‘D’ and group ‘P’ according to computer generated randomization table.

Exclusion criteria for the above study are patients with cardiovascular disease, epilepsy, COPD, hypertension, on antipsychotics and difficult airway.

Table 1: Demographic profile

|                | Group ‘D’        | Group ‘P’        | ‘p’ value |
|----------------|-----------------|-----------------|----------|
| Age of pts( yr) mean | 34.8±9.6        | 34.4±9.8        | 0.84 (NS) |
| Gender of pts (M:F), mean | 21:29           | 20:30           | 0.86 (NS) |
| Wt. of patients (kg) | 55.7±6.75       | 54.6±5.45       | 0.39     |
| ASA(1/2)        | 66:34           | 72:28           | 0.52     |

Chi Square test,  
*<0.05, significant, NS-not significant

I.V. access was secured and i.v. fluid, Ringer Lactate (500 ml) was given. Pre-oxygenation was done for 3 minutes after attaching all basic vital monitors like pulse-oximeter, ECG, NIBP and EtCO2. Basal parameters like SpO2, HR and MAP were recorded. All patients received premedication which included inj. glycopyrrolate 10µ/kg and inj. Fentanyl 2µ/kg according to body weight.

Group D patients received inj.Dexmedetomidine 1µg/kg in 100 ml 0.9% normal saline over 20 minutes prior to induction while group P patients received plain 0.9% normal saline over 20 minutes.

Induction was done with inj. Propofol 2mg/kg, relaxed with inj. Succinyl choline and intubated orally with appropriate sized cuffed ETT by anaesthesiologist (experienced >5 years). Anaesthesia was maintained with O2 (33%) and N2O (66%), volatile anaesthetic like isoflurane and maintenance fluid Dextrose normal saline was given at 4-6 ml/kg/hr. After the procedure the patient was extubated with reversal (inj.Neostigmine+ inj. Glycopyrrolate) being given depending upon body weight. Intra-op parameters recorded are MAP, HR at 0 minutes and 5 minutes of intubation. Other vital parameters like parameters like SpO2, etCO2 were monitored.

Statistical analysis was carried out using SPSS version 17.

Results

All data are mentioned in terms of mean and standard deviation (S.D.). The demographic profile (chi square test) was comparable with no significant difference between two groups as shown in table 1.

The MAP and HR (Unpaired ‘t’ test) were significantly lower in group ‘D’ during laryngoscopy and 5 minutes later with highly significant p value of <0.001 as compared to placebo as shown in table 2 and table 3 respectively.

Side effects of dexmedetomidine

1. Hypotension and bradycardia
2. Hypertension after loading dose
3. Dystonic movements
4. Dry mouth, tachycardia, atrial fibrillation
5. Nausea and vomiting, haemorrhage, acidosis
6. Confusion, agitation and rigors (rare)

In 2006, Hepsev A et al.,2 did a randomized control study and concluded Dexmeditomidine as a reliable premedication.

In 2012, Poonam S Glodki et al.,3 conducted a similar study and found that Dexmeditomidine is an effective anaesthetic adjuvant that can be safely used in laparoscopic surgeries.

We compared dexmedetomidine with placebo to attenuate pressor response for direct laryngoscopy under general anaesthesia.

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Table 2: Variation in heart rate

|                  | Group ‘D’ (Mean±S.D.) | Group ‘P’ (Mean±S.D.) | ‘p’ value |
|------------------|-----------------------|-----------------------|-----------|
| Baseline         | 82.3±12               | 79.1±7.5              | 0.11      |
| After intubation(0 min) | 73.2±9.7           | 84.9±8.2              | 0.00**    |
| 5 mins           | 69.9±8.3              | 83.5±7.3              | 0.00**    |

Unpaired ‘t’ test
*<0.05, significant

Table 3: Variation in map (Mean Arterial Pressure)

|                  | Group ‘D’ (Mean±S.D.) | Group ‘P’ (Mean±S.D.) | ‘p’ value |
|------------------|-----------------------|-----------------------|-----------|
| Baseline         | 90.8±3.4              | 91.8±3.4              | 1.00      |
| After intubation(0 mins) | 83.8±9.2          | 96.9±5.5              | 0.00**    |
| 5 mins           | 79.9±7.9              | 95.6±6.7              | 0.00**    |

Unpaired ‘t’ test
*<0.05, significant
** p <0.001, highly significant

Graph 1: Heart rate comparison

Graph 2: Map comparison
Discussion
In the past, numerous studies have been tried with high dose opioids for attenuating pressor response.

α2 receptors are located in post synaptic terminals in CNS, which causes decreased neuronal activity and augmentation of vagal activity. The role of α2 receptor agonists in sympatholytic action is by decreasing release of catecholamines from sympathetic nerve terminals.

In our study, we have observed that infusion of Dexmedetomidine at 1µg/kg over 20 minutes before induction has decreased the pressor response but not completely obviated it by decrease in basal heart rate and MAP to 9 beats per minute (bpm) and 7 mm of hg respectively as compared to group ‘p’ where they have received only saline with increase in HR and MAP to 6bpm and 5 mmm of hg respectively.

Various authors have found similar response to I.V. Dexmedetomidine after intubation.4,7

Basar et al.,5 observed a increase in HR by 5 bpm in control group and decrease in HR by 5 bpm in Dexmedetomidine group after intubation.

In 2010, similar study by Ferdi et al.,7 in patients undergoing fast track coronary artery bypass grafting concluded that dexmedetomidine can be safely used to attenuate the haemodynamic responses to endotracheal intubation in patients undergoing myocardial revascularization receiving beta blockers.

Similar study by Dr. Sukhwinder Jit Singh et al.,8 conducted on 100 patients to evaluate pressor response showed comparable results with decrease in heart rate response by 10-15% in dexmed group and increase in heart rate by 15-25% in placebo group.

Jaakola et al.,9 have observed a fall by 17mm Hg in SBP 5 min after intubation in Dexmed group and in control group an increase in SBP by 10mm Hg compared to basal values. This compares with our study.

In 2010 Osman Ilhan et al.,10 did a randomised double blind prospective clinical study, 30 ASA I and II patients undergoing intracranial tumour surgery. In Group D, dexmedetomidine was infused as a 1mcg/kg bolus dose 10 mins before induction and maintained with 0.4mcg/kg/min during operation. In group F fentanyl 0.02mcg/kg/min was given as an infusion for anaesthesia maintenance. At induction fentanyl was given as a 2mcg/kg dose in group D and 4mcg/kg dose in group F. Haemodynamic changes were recorded. In group D, MAP and HR values after intubation, after skull clamp insertion and after extubation were lower than in group F. It was concluded that dexmedetomidine is safer and more effective in controlling haemodynamic changes during surgical stimulation than the standard agents used in neuroanaesthesia.

In 1990, Aanta et al.,11 conducted a similar study on vigilance, thioental requirements and haemodynamic, catecholamine and hormonal responses to surgery in 40 ASA I nonpregnant females posted for dilatation and curettage (D and C) of uterus. Patients randomly received i.v. either 0.5 µg/kg body weight dexmedetomidine or same amount of saline as premedication. ECG, heart rate and non invasive systolic and diastolic arterial blood pressure were recorded at 5 min interval. Authors observed that, 10 min after dexmedetomidine administration there was an average decrease of 10% in SBP and DBP after dexmedetomidine administration.

In 1992, Scheinin B et al.,12 conducted a study on 24 ASA I patients to know hormonal responses to tracheal intubation. This study found the decrease in heart rate within 10 seconds of laryngoscopy and at 5 minutes after tracheal intubation but not immediately after intubation and this difference is probably because of lower dose of dexmedetomidine infusion.

Keniyta et al.,13 noted a reduction of 20mm Hg SBP compared to the basal value which concurs with our study.

Also a study by Lakshmi Mahajan et al., showed a better attenuation of pressor response in dexmed and magnesium sulphate group as compared to placebo group at BIS (Bi-Spectral) value of 40-60 (pre induction).14

Side effects like bradycardia (heart rate<50 bpm) which is very concerning to an extent where usage of atropine (0.01 mg/kg) is recommended has not been encountered in our study.

The incidence of bradycardia may be less or not concerning in our study may be because of smaller dose of infusion of dexmed as compared to other studies where they have highlighted the incidence of bradycardia and dexmed infusion dose ranging from 1-10µg/kg/hr15.

Study by Erkola et al., have shown in their study that bradycardia was more common in those patients premedicated with dexmedetomidine than those premedicated with midazolam and this difference is mostly because dexmed was used at rate of 2µg/kg/hr.

One more study by SY Hussain et al., has shown there was incidence of severe bradycardia who were excluded from the study.16

We conclude from our study that dexmedetomidine infusion before intubation is very efficacious in decreasing the pressor response during direct laryngoscopy and intubation which is a major concern for every anaesthesiologist and also challenging.

The limitation of our study was we have compared dexmedetomidine with placebo. In order to evaluate its efficacy it is better to compare with proven drugs like xylocard / β blockers / clonidine.

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Ethical approval: The study was approved by the Institutional Ethics Committee.
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