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Dr. Prashanth Kumar C
B Associate Professor,
Department of Anesthesiology,
Srinivas Institute of Medical Sciences and Research Centre,
Mukka, Mangalore,
Karnataka, India

Dr. Veena A Shetty
Associate Professor,
Department of Anesthesiology,
Srinivas Institute of Medical Sciences and Research Centre,
Mukka, Mangalore,
Karnataka, India

Corresponding Author:
Dr. Veena A Shetty
Associate Professor,
Department of Anesthesiology,
Srinivas Institute of Medical Sciences and Research Centre,
Mukka, Mangalore,
Karnataka, India

Study of adverse effects of different doses of dexmedetomidine when used with propofol: A comparative randomised controlled study

Dr. Prashanth Kumar C and Dr. Veena A Shetty

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Abstract
Adverse Effects like Bradycardia and hypotension are the most common side-effects and can be described as an adverse exaggeration of their clinical advantages. Severe bradycardia leading to cardiac arrest has been reported with the use of dexmedetomidine. Other reported side effects are hypertension, nausea, vomiting, dry mouth, atrial fibrillation, pyrexia, chills, pleural effusion, atelectasis, pulmonary edema, hyperglycemia, hypocalcaemia, acidosis, etc. Rapid administration of dexmedetomidine infusion (loading dose of 1 µg/kg if given in less than 10 minutes) may cause transient hypertension. This study is an effort to find if there are any adverse effects of different doses of dexmedetomidine when used with propofol.

Keywords: Adverse, Reactions, Complications, Dexmedetomidine.

Introduction

Intravenous dexmedetomidine is associated with a biphasic BP response [1]. At low doses the dominant action of α2 adrenoreceptor agonist activation is a reduction in sympathetic tone, mediated by a reduction of noradrenaline release at the neuroeffector junction, and a inhibition of neurotransmission in sympathetic nerves [2]. The net effect of dexmedetomidine action is a significant reduction in circulating catecholamine's with a slight decrease in BP and a modest reduction in heart rate. When administered as a continuous infusion, it is associated with a stable hemodynamic response. Significant hypotension is usually only observed in patients with pre-existing hypovolemia or vasoconstriction. The bradycardia frequently seen after the administration of dexmedetomidine may be due to the central sympatholytic action, enhanced vagal activity and partly by baroceptor reflex. Hemodynamic stability provided by α2 17 adrenoceptor agonists in the perioperative period leads to a reduction in perioperative myocardial ischemia [1].

Central Nervous System: Cerebral Blood Flow and Metabolism High dose dexmedetomidine can cause marked decrease in cerebral blood flow (CBF) without proportional decrease in cerebral metabolic rate. Cerebrovascular dilation induced by inhalational agents was found to be of a lesser extent when dexmedetomidine was used as a premedication [2]. Intracranial Pressure α2 agonists are vasoconstrictors more on the venous than on the arteriolar vasculature. Since the venous compartment occupies most of the cerebral blood volume, α2 agonists theoretically should decrease intra cranial pressure. Clinical trials in head-injured patients, however, have not reflected these observations [2]. Effect on EEG The α2 agonists mimic pattern of increasing depth of anaesthesia by attenuating the α and β fractions and total power of an EEG as well as increased slow wave activity. An infusion of 0.6 µg/kg/hour has been reported to produce EEG changes that correspond to a bispectral index (BIS) of 60. However volunteers were readily awakened simply by talking to them. It also reduces seizure threshold in animal models but there are no reports of seizures in humans [2]. Effect on Evoked Potentials A study in human volunteers demonstrated that, in contrast to most anaesthetics, dexmedetomidine does not decrease cortical responses. It could be due to indirect cortical depression caused by reduced activity from subcortical areas. Dexmedetomidine can be used for neurophysiological monitoring in circumstances in which neural tissue is at risk for injury. [2] Neuroprotection Animal studies have shown that dexmedetomidine improves neuronal survival after transient global or focal cerebral

ischemia. It has been hypothesised that neuroprotection is due to balance between proapoptotic and antiapoptotic proteins and reduction of excitotoxicity [2]. Respiratory effects Even at high doses, dexmedetomidine does not suppress respiratory function and has no adverse effects on respiratory rate and gas exchange [3]. It helps in maintaining sedation without respiratory depression. It hence may facilitate weaning and extubation in intensive care unit (ICU), especially in patients who have failed previous attempts at weaning because of agitation and hyperdynamic cardiopulmonary response [4, 5].

Endocrine and renal effects Dexmedetomidine activates peripheral presynaptic α2 adrenoreceptors which reduces the release of catecholamines, and hence attenuate sympathetic response to surgery [6]. α2 agonists exert a diuretic effect by inhibiting action of vasopressin at the collecting duct. They also enhance osmolal clearance through vasopressin independent pathways, possibly mediated by the α2b receptor. [7] The teratogenic effects of dexmedetomidine have not been adequately studied at this time, but the drug crosses the placenta. Thus it should be used only if the risk to foetus is justified [8].

Adverse Effects like Bradycardia and hypotension are the most common side-effects and can be described as an adverse exaggeration of their clinical advantages [9]. Severe bradycardia leading to cardiac arrest has been reported with the use of dexmedetomidine [10] Other reported side effects are hypertension, nausea, vomiting, dry mouth, atrial fibrillation, pyrexia, chills, pleural effusion, atelectasis, pulmonary edema, hyperglycemia, hypocalcaemia, acidosis, etc. Rapid administration of dexmedetomidine infusion (loading dose of 1 µg/kg if given in less than 10 minutes) may cause transient hypertension [11]. This study is an effort to find if there are any adverse effects of different doses of dexmedetomidine when used with propofol.

Aims and Objectives

To study the complications when dexmedetomidine when used with propofol.

Materials and Methods

Source of data

This study was conducted on 400 patients posted for elective surgery under general anaesthesia in Srinivas Institute of Medical Sciences, Mukka, Mangalore.

The study was conducted from 1/10/2017 to 1/06/2019.

Inclusion criteria

The following patients were included for the study –

Patients of ASA physical status (PS) I & II scheduled to undergo elective surgery under general anaesthesia

Adults aged between 18-60 years

Exclusion criteria

The exclusion criteria for the study are

- Known history of sensitivity and contraindications to drugs used in the study
- History of hypertension
- Anticipated difficult airway
- Patients requiring nasal intubation
- Patients on long term analgesics, narcotics & antipsychotics
- Patients who required more than 1 attempt for intubation
- Patients who were having inadequate depth of anaesthesia during intubation

Patients were randomly allocated to one of the four study groups i.e.

group A,B,C,D by computer generated sequence to receive a study

drug diluted to 20 ml via an infusion pump over 20 minutes.

Group A received 1 µg/kg of dexmedetomidine.

Group B received 0.6 µg/kg of dexmedetomidine.

Group C received 0.3 µg/kg of dexmedetomidine.

Group D received 20 ml of normal saline.

It was given over an infusion of 20 minutes.

Patients were pre oxygenated for 3 minutes during the remaining last 3 minutes of infusion of the study drug. Once the infusion was completed fentanyl 2 µg/kg was given intravenously over 1 minute. Induction was done with propofol at the rate of 80 mg/kg/hour via an infusion pump.

- Dose of propofol for loss of verbal contact and loss of eyelash reflex was noted.
- After confirming adequate mask ventilation, patients were paralysed with Inj. atracurium 0.5 mg/kg and patients were ventilated for 3.5 minutes. Direct laryngoscopy was done by an anaesthesia consultant with minimum of 2 years experience and patients were intubated with a cuffed endotracheal tube of appropriate size.

Intubation time was noted from the time of introduction of laryngoscope into the mouth till it was taken out and number of attempts for intubation was recorded. Intubation conditions and complications were noted. Anaesthesia was maintained with oxygen, nitrous oxide, isoflurane and relaxant top ups as needed. Patients were monitored throughout the procedure. After the completion of surgery and return of spontaneous respiratory attempts along with presence of more than 2 twitches on train of four stimulation, neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg.

- Extubation was performed after achieving standard extubation criteria.
- Complications were noted.

Results and Discussion

Bradycardia

We noted bradycardia during laryngoscopy and intubation in 2 patients in group A (2%), 3 in group B (3%), 4 in group C (4%) and 1 patient in group D (1%). Following our protocol, we treated these patients with atropine. Hence these patients were excluded from hemodynamic analysis. Turgut *et al*. (2008) noted bradycardia in 20% of their patients with bolus dose of dexmedetomidine 0.6 µg/kg pre induction followed by 0.2 µg/kg/hour infusion. This higher incidence in their study could be attributed to dexmedetomidine infusion following a bolus dose. Keniya *et al*. (2011) noted bradycardia intraoperatively needing atropine in two among 60 patients (6.6%) who had received dexmedetomidine 1µg/kg prior to induction. They did not observe any fall in BP. One patient out of these two, exhibited bradycardia in the postoperative period as well. Both the studies haven't specified if there was a preceding event leading to the bradycardia. Incidence of bradycardia in our study was 2.5% inclusive of all groups. The incidence in each group was also lower than the values quoted in the above study (Group A- 2%, group B- 3%, group C- 4%, group D- 1%). This lower incidence could be attributed to

the fact that the study drug was infused over 20 minutes prior to induction and we did not use dexmedetomidine as a continuous infusion after the loading dose. Talke *et al*. (2000) evaluated dexmedetomidine, for its ability to attenuate stress responses during emergence from anaesthesia after major vascular operations. Patients were randomized to receive an IV infusion of dexmedetomidine or placebo starting 20 minutes before the induction of anaesthesia and continuing to 48 hours after surgery. They noted one episode of sinus pause during intubation lasting for 5 to 10 seconds that resolved spontaneously among 22 subjects. Similarly, we noted bradycardia occurring during laryngoscopy and endotracheal intubation in our study. Pipanmekaporn and co-workers (2013) studied the effect of dexmedetomidine on hemodynamic responses to double lumen tube intubation and assessed the adverse effects related to dexmedetomidine. They noted that among 30 patients who received dexmedetomidine (0.7 µg/kg), 2 patients had bradycardia. These patients received atropine 0.3 mg as a rescue measure to which bradycardia reverted similar to our study. They concluded that bradycardia can occur frequently in patients receiving an initial bolus of dexmedetomidine especially with rapid administration and also in those with concurrent negative chronotropic medications. Basar H *et al*. (2008) reported that the incidence of bradycardia after a single dose of 0.5 µg/kg of dexmedetomidine was about 5%. This was almost ten times higher than the incidence reported in our study. 78 This could be attributed to the drug being given as a bolus in their study.

Desaturation

We noted a reduction in room air saturation during the study drug infusion in 1 patient in group A, two patients in group B and group C each. Administration of 100% oxygen via Bain's breathing system was sufficient to revert the drop in saturation and none of them required assisted for ventilation as per the protocol. None of these patients had loss of consciousness or airway compromise during this period of saturation drop. Mason *et al*. (2013) conducted a study to determine the safety and efficacy of dexmedetomidine for procedural sedation in 669 children. They administered dexmedetomidine as an intravenous bolus (2 µg/kg) over a 10minute period followed by infusion at a rate of 1 µg/kg/hour. They noted in their study that six (0.9%) of them had brief periods of oxygen desaturation below 95% which did not require airway intervention. Ramsay MA and co-workers (2004) reported a series of three cases where they used dexmedetomidine as a total intravenous anaesthetic agent. They administered dexmedetomidine as a loading dose of 1µg/kg followed by an infusion of 0.7 µg/kg/hour. The infusion was increased to 5 µg/kg/hour to a period of five minutes to achieve adequate depth. They noted that in one of the patient the airway was compromised requiring manual support in the form of a chin lift to maintain his airway. This occurred when they increased the dose of dexmedetomidine to achieve a desired depth of anaesthesia. However the respiratory drive remained intact. They concluded that level of sedation at which airway control is lost has not been well studied and that this may occur at lower doses of dexmedetomidine as well. Harsoor *et al*. (2013) conducted a study comparing IV dexmedetomidine (loading dose of 0.5 µg/kg followed by infusion 0.5 µg/kg/h) and normal saline in terms of their effects on sensory, motor, hemodynamic parameters and sedation during subarachnoid block. During the study they noted that respiratory rate was lower with dexmedetomidine group but oxygen saturation remained comparable to normal saline.

Inadequate Depth of Anaesthesia

We noted that muscle relaxation and depth of anaesthesia was inadequate in 3 patients in group A, 2 in group B, 3 in group C, 4 in group D who were excluded from analysis of hemodynamic variations. The patients moved during laryngoscopy and intubation in spite of achieving the loss of eyelash reflex and verbal response, a standard end point of titration for propofol induction. We had also used adequate 0.5 mg/kg of atracurium for muscle relaxation and laryngoscopy was performed after 3.5 minutes of drug administration. Additional doses of propofol were administered to these patients. The increased blood pressure and heart rate responded to this additional dose of propofol.

Second Intubation Attempt

2 patients in group A, 2 patients in group B, 2 patients in group C, 4 patients in group D required a second attempt of laryngoscopy and intubation and hence were excluded from the study. They accounted for 2.5% of the total sample population incidence, which is similar to the reported incidence in other studies.

Hypertension

Intraoperative hypertension was noted in one patient in group A which was seen after the time period of the study. The hypertension was treated with titrated doses of nitroglycerine. Transient hypertensive response has been observed with higher doses of (1 to 4 µg/kg) dexmedetomidine. This is attributed to initial stimulation of α2B receptors present in vascular smooth muscles. This hypertension normalizes once there is decrease in central sympathetic outflow due to α2A action. 87 Younger children and multiple bolus therapies are highly significant predictors of the occurrence of hypertension with dexmedetomidine. This rise in blood pressure in our study could be attributed to surgical stimulation itself as this occurred 60 minutes after completion of dexmedetomidine infusion and no similar response is seen in any other group including the control group.

Hypotension

Intraoperative hypotension was noted in one patient in our study in group B. It was noted 40 minutes after intubation and treated with fluids and ephedrine 6mg bolus dose. Rebecca Y. Klinger and co-workers (2012) evaluated hemodynamic impact of dexmedetomidine administration in 15,656 non-cardiac surgical cases. They found that there was no significant difference in the overall incidence of intraoperative hypotension due to dexmedetomidine. Pipanmekaporn T and co-workers (2013) noted hypotension in 13% of their patients who were treated with fluids and ephedrine. The increased incidence of hypotension in their study might be attributed to the fact that patients underwent thoracic surgery which could have been associated with substantial blood loss.

Conclusion

We conclude that 1 µg/kg and 0.6 µg/kg of

dexmedetomidine offer the best choice without much complications.

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