EVALUATION OF THE EFFECTS OF DIFFERENT DOSES OF DEXMEDETOMIDINE ON INDUCTION DOSE OF PROPOFOL

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ABSTRACT

BACKGROUND AND OBJECTIVES

Dexmedetomidine, a potent and highly selective α2-adrenoreceptor agonist, possesses desirable properties like sedation, analgesia, sympatholysis and reduces the anaesthetic requirement. Bradycardia and hypotension are the most common side effects of dexmedetomidine. Propofol, currently the most popular induction agent due to its beneficial effects such as suppression of airway reflexes, fast recovery, etc., has the same side effects during induction of anaesthesia. Hence, titration of the above-mentioned drugs can minimise the adverse and retain the desired effects of their pairing. Various loading dosages of dexmedetomidine ranging from 0.33 to 1 µg/kg have been used in pre-induction. Hence, this study was conducted with an objective of comparing and evaluating the effects of different doses of dexmedetomidine on induction dose of propofol and haemodynamics.

MATERIALS AND METHODS

400 patients of ASA physical status I and II, aged 18 to 60 years, undergoing general anaesthesia requiring oral endotracheal intubation were randomly allocated into 4 groups- Group A, B, C received dexmedetomidine 1 µg/kg, 0.6 µg/kg, 0.3 µg/kg respectively, while group D received normal saline. The study drug was diluted to a 20 mL solution and infused over 20 minutes. The sedation was assessed using Brussels Sedation Scale during the same period. Anaesthesia protocol included fentanyl 2 µg/kg, propofol infusion at 80 mg/kg/hour, atracurium 0.5 mg/kg, endotracheal intubation, maintenance with oxygen, nitrous oxide and isoflurane. Dose of propofol for loss of eyelash reflex and verbal response, duration of laryngoscopy and number of intubation attempts were noted. Modified Aldrete's Score was noted immediately and 10 minutes after extubation.

RESULTS

During the study, we noted that 72.5% of subjects in group A and 65.6% in group B were sedated but arousable with verbal stimuli, at the end of infusion as compared to 18.3% in group C and 3.3% in group D. We observed a reduction in propofol requirement for the loss of verbal response with dexmedetomidine which was 0.93 mg/kg, 1.08 mg/kg, 1.29 mg/kg with group A, group B, group C respectively, while group D (saline) required 1.64 mg/kg propofol.

CONCLUSION

Dexmedetomidine reduced the induction dose of propofol; a maximum reduction was seen along with 1 µg/kg followed by 0.6 µg/kg and 0.3 µg/kg. Attenuation of haemodynamic response was best seen with 1 µg/kg followed by 0.6 µg/kg while hemodynamic profiles of 0.3 µg/kg of dexmedetomidine and placebo group were similar. Hence, we conclude that 1 µg/kg and 0.6 µg/kg of dexmedetomidine offer a reduction in anaesthetic requirement along with desirable haemodynamics.

KEYWORDS

Evaluation, Doses of Dexmedetomidine, Induction Dose of Propofol.

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INTRODUCTION: The modern definition of anaesthesiology provided by the American Board of Anaesthesiology states that anaesthesiology is the practice of medicine providing insensibility to pain during surgical, obstetric, therapeutic and diagnostic procedures.[1] General anaesthesia is a drug induced, controlled and reversible loss of consciousness during which patients are not arousable, even by painful stimulation. It is associated with impairment of the ability to independently maintain a patent airway.[2] Laryngoscopy and endotracheal intubation marked a new era in the development of anaesthesia resulting in effective control of airway and ventilation.[3] Airway management is the cornerstone of anaesthesia, emergency and critical care practice. Endotracheal intubation is a rapid, simple, safe and a non-surgical technique that fulfils all the objectives of airway management and remains the gold standard of airway management in spite of availability of several other

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devices (notably supraglottic devices) for securing and maintaining airway.[4]

Reflex sympathetic stimulation in the form of tachycardia and hypertension associated with laryngoscopy and endotracheal intubation is called pressor response. In paediatric age group, bradycardia seen during airway manipulation is a corresponding response. This response is directly related to the force and duration of laryngoscopy. The pressor response caused by endotracheal intubation may alter the balance between myocardial oxygen demand and supply. Hence, laryngoscopy and intubation can precipitate myocardial ischaemia in patients with compromised cardiovascular system.[5] The cardiovascular responses are due to stimulation of proprioceptors as a result of airway manipulation.[6] Glossopharyngeal and vagal nerves transmit impulses to the brain stem, which cause activation of both the sympathetic and parasympathetic nervous systems. Hypertension and tachycardia mediated by sympathetic system involves the cardio accelerator fibres, sympathetic ganglia and catecholamines. A part of response is also due to renin-angiotensin system.[7]

Many methods, drugs and techniques have been evaluated to attenuate the pressor response to laryngoscopy and intubation with a goal of abolishing or minimising the deleterious consequences.

Propofol, barbiturates, and benzodiazepines are all associated with profound haemodynamic adverse effects at doses needed to attenuate response to laryngoscopy and intubation.[8] As it is impractical to achieve sufficient depth to prevent sympathetic response to intubation solely with a single agent, adjuvants like opioids, β blockers, calcium channel blockers, vasodilators, etc., are used.[9] It is essential to remember that time of laryngoscopy and intubation should coincide with the peak effect of agents used to minimise haemodynamic stimulation. Opioids are widely used adjuvants and appear to give a graded response in blunting haemodynamic responses. While 2 μg/kg of fentanyl given before induction partially attenuates cardiovascular response, higher doses that prevent a haemodynamic response to intubation are associated with risk of adverse effects.[10] A bolus of 1.5 mg/kg of lignocaine given intravenously adds 0.3 MAC of anaesthetic potency and can blunt haemodynamic responses to intubation.[11] Kasten and co-workers (1986) showed that lignocaine administered (3 mg/kg) intravenously is associated with significant attenuation of haemodynamic response to endotracheal intubation.[12] α2 agonists like clonidine have been used extensively in the past for attenuation of sympathoadrenal stimulation caused by tracheal intubation and surgery. They have the desirable properties of sedation, anxiolysis, and analgesia with no respiratory depression. In addition, α2 agonists also have sympatholytic and anti-nociceptive effects that contribute to haemodynamic stability during surgical stimulation. They also reduce the dose requirement of intravenous and volatile anaesthetics.[13] Dexmedetomidine is a potent and highly selective α2 adrenoreceptor agonist, which was approved for clinical use in 1999 and recently introduced in India. It has all the above-mentioned properties and can impart significant benefits in the peri-operative use.[13] In spite of the multiple desirable effects of dexmedetomidine, bradycardia and hypotension remain clinically significant adverse effects. High doses of dexmedetomidine can result in a decreased heart rate and cardiac output, with a biphasic dose response relation for BP. High doses of dexmedetomidine can also be a cause of systemic and pulmonary hypertension. The most common side effect during induction of anaesthesia with propofol is hypotension. The haemodynamic changes from propofol administration depend on the ability of the compensatory mechanisms to respond to changes and the concomitant use of any other drugs. Since a combination of propofol and dexmedetomidine can cause both beneficial and adverse effects on the patient, it would be ideal to titrate the dosage of dexmedetomidine to retain its desirable effects while negating its side effects. Different doses of dexmedetomidine have been used with an induction agent for attenuation of haemodynamic response to intubation.

In this study, we compared and evaluated the different doses of dexmedetomidine for the effect on induction dose of propofol.

AIMS AND OBJECTIVES: To compare and evaluate the different doses of dexmedetomidine for the effect on induction dose of propofol.

MATERIALS AND METHODS:

Source of Data: This study was conducted on 400 patients posted for elective surgery under general anaesthesia at ESIC Medical College, Gulbarga, Karnataka after getting the institutional ethical clearance. The study was conducted for a period of one year from March 2014 to April 2015.

Inclusion Criteria:

- Patients of ASA physical status (PS) I & II scheduled to undergo elective surgery under general anaesthesia.
- Adults aged between 18-60 years.

Exclusion Criteria:

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

Method of Collection of Data:

- A sample size of 100 per group was taken.
- Thorough pre-anaesthetic evaluation was done a day before the surgery.
- A written informed consent was taken.
- All the patients were kept nil per oral as per standard guidelines.
- After shifting the patient to OT, wide bore IV access was secured and crystalloid infusion was started. The study drug was prepared by a designated anaesthesia technician who was not present at the time of administering the drug. 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.
  1. Group A received 1 µg/kg of dexmedetomidine.
  2. Group B received 0.6 µg/kg of dexmedetomidine.
  3. Group C received 0.3 µg/kg of dexmedetomidine.
  4. Group D received 20 mL of normal saline.

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. Anaesthesia was maintained with oxygen, nitrous oxide, isoflurane and relaxant top-ups as needed.

Brussels sedation scale and Propofol dose was recorded by a person who was unaware of the nature of the study.

Patients were monitored throughout the procedure.

Statistical Analysis was done using Statistical Package for the Social Sciences ver. 16 (IL, Chicago). Analysis of variance (ANOVA) with repeated measures was used to study the differences of continuous variables between the two groups. Posthoc Tukey test was used for intergroup comparison of variables. Categorical variables were analysed with chi-square test and Fisher exact test, $p<0.05$ was considered statistically significant.

RESULTS:

Weight Distribution: All the four groups were comparable in terms of weight. There was no significant statistical difference in between groups (p=0.21).

Group	Mean (kg)	F	Significance(p)
A	52.16	1.515	0.21
B	54.74		
C	55.25		
D	53.76		

Table 1: Weight Distribution

Gender Distribution: Statistically, there were significantly more number of males when compared to females.

Group	Gender	Frequency	%
Group A	F	37	40.7
	M	54	59.3
Group B	F	22	22.9
	M	74	77.1
Group C	F	35	37.6
	M	58	62.4
Group D	F	42	45.7
	M	50	54.3

Table 2: Gender Distribution

ASA Physical Status: There was no significant statistical difference between groups in terms of ASA PS.

In groups A, B, C, D; 97.8%, 95.8%, 94.6%, 96.7% of patients belonged to ASA PS I respectively.

In groups A, B, C, D; 2.2%, 4.2%, 5.4%, 3.3% of patients belonged to ASA PS II respectively.

There was no statistical difference between groups in terms of ASA PS (p=.708).

Age Distribution: There is no significant statistical difference in terms of age in between groups (p=0.76).

Age Distribution				
Group	**Mean (years)**	**Std. Deviation**	**F**	**Significance (p)**
A	32.03	11.22	2.313	0.076
B	31.07	9.611		
C	32.22	10.643		
D	35	11.342		

Table 3: Age Distribution

Brussels Sedation Scale at 10 Minutes: Brussels Sedation Scale at the end of 10 minutes showed significantly different scores in the four groups ($p<0.001$). 2.2% of subjects in group A were deeply sedated and responded only to painful stimuli (score=2) whereas group B, C, D did not have any patient with score at 2 at 10 minutes. 39.6% of people in group A were sedated but arousable with verbal stimuli (score=3), compared to 26% in group B, 9.7% in group C and 2.2% in group D.

At the end of ten minutes, 58.2%, 74%, 90.3%, 97.8% of the patients were awake (score =4) in group A, B, C and D respectively.

Group		Sedation Score		
		2	3	4
A	Count (% within group)	2(2.2%)	36(39.6%)	53(58.2%)
B	Count (% within group)	0	25(26.0%)	71(74.0%)
C	Count (% within group)	0	9(9.7%)	84(90.3%)
D	Count (% within group)	0	2(2.2%)	90(97.8%)

Table 4: Brussels Sedation Scale at 10 minutes

Fisher's exact test for Brussels Sedation Scale at 10 minutes		
	Value	Significance (p)
Fisher's exact test	57.838	<0.001

Table 5: Fisher's exact test for Brussels Sedation Scale at 10 Minutes

Brussels Sedation Scale 20 minutes Post-Infusion: Sedation assessed by Brussels Sedation Scale at the end of 20 minutes, was significantly different in the four groups (p<0.001). In group A, 1.1% of the subjects were not arousable (score=1) whereas none of thesubjects in other groups had a score of 1.

In group A, 13.2% of subjects and in group B, 5.2% were deeply sedated and responded only to painful stimuli (score = 2). No patients in group C and D had a score of 2. 72.5% of people in group A were sedated but arousable with verbal stimuli (score=3) compared to 65.6% in group B, 18.3% in group C, 3.3% in group D.

Number of subjects who were awake (score=4) at the end of ten minutes were 13.2% in group A, 29.2% in group B, 78.5% in group C and 96.7% in group D.

Group		Sedation Score			
		1	2	3	4
A	Count (% within group)	1(1.1%)	12(13.2%)	66(72.5%)	12(13.2%)
B	Count (% within group)	0	5(5.2%)	63(65.6%)	28(29.2%)
C	Count (% within group)	0	3(3.2%)	17(18.3%)	73(78.5%)
D	Count (% within group)	0	0	3(3.3%)	89(96.7%)

Table 6: Brussels Sedation Scale 20 minutes Post-infusion

Fisher's exact test for Brussels Sedation Scale 20 minutes Post-infusion		
	Value	Significance (p)
Fisher's exact test	201.482	<0.001

Table 7: Fisher's exact test for Brussels Sedation Scale 20 minutes Post-infusion

Mean duration of intubation in groups A, B, C and D were 10.91 seconds, 10.687 seconds, 10.602 seconds, and 10.59 seconds respectively.

There was no statistically significant difference in between groups (p=0.165).

	Group	Mean (seconds)	F	Significance (p)
Duration	A	10.9121	1.14162	1.986
	B	10.6875	1.0189	
	C	10.6022	1.10473	
	D	10.5978	1.04891	

Table 8: Duration of Laryngoscopy and Intubation

Propofol Dose: There is significant intergroup difference between the four groups for induction dose of propofol (p<0.001). Mean propofol dose for loss of eyelash reflex in the groups A, B, C and D were 48.63 mg, 59.48 mg, 71.51 mg and 88.42 mg respectively. Similarly, the mean propofol dose for loss of verbal response in the groups A, B,C and D were 47.97 mg, 58.7mg, 71.72 mg were 88.75 mg respectively. Significant differences existed between all groups (<0.001).

Propofol dose(mg)	Group	Mean (mg)	Std. Deviation	Significance (p)
For loss of eyelash reflex	A	48.63	16.246	<0.001
	B	59.48	21.095	
	C	71.51	25.79	
	D	88.42	20.886	
For verbal response	A	47.97	15.184	<0.001
	B	58.7	21.067	
	C	71.72	26.728	
	D	88.75	21.299	

Table 9: Propofol Dose

DISCUSSION: In our study, we observed the sedation quality during the period of infusion of the study drug and analysed associated complications during the same. Sedation was assessed by Brussels Sedation Scale midway during the infusion and upon completion of infusion of the study drug, Sedation scores were significantly different between the four groups at both the time intervals. ($p<0.001$).

Keniya et al (2011) conducted a study evaluating effects of dexmedetomidine 1 µg/kg on endotracheal intubation and anaesthetic requirement. They reported that patients were drowsy but arousable after 10 minutes of receiving dexmedetomidine.[14] Ghodki et al (2012) evaluated the effects of dexmedetomidine as an anaesthetic adjuvant in laparoscopic surgery.

They used dexmedetomidine as a loading dose of 1 µg/kg followed by infusion of 0.2 µg/kg/hour. They observed a 20% reduction in entropy to reach a value between 60 and 80 after infusing the loading dose of dexmedetomidine. These patients were sedated but arousable by verbal commands at that point of time indicating good sedation.[15] We had similar findings in our study.

Propofol Dose: There was significant intergroup difference between the four groups in terms of propofol requirement for induction ($p<0.001$). Mean propofol dose for loss of eyelash reflex and verbal response was 48.63 mg (0.93 mg/kg) and 47.97 mg (0.91 mg/kg) respectively in group A. This was much lesser than the dose needed in the control group (1.64 and 1.65 mg/kg for loss of eyelash reflex and verbal response). Ghodki et al (2012) noted that mean dose of propofol required for induction was 37.5 mg (0.75 mg/kg) with 1 µg/kg of dexmedetomidine IV given pre-induction.[15] However, they noted the dose of propofol needed to achieve entropy of 40-60 as compared to loss of verbal response and eyelash reflex in our study.

Similar decrease in induction dose of thiopentone was noted by Scheinin et al (1992)[16] and Basar H et al (2008)[17] in their study where they used 0.6 µg/kg and 0.5 µg/kg dexmedetomidine. Aho et al (1991) noted that there was negligible difference in anaesthetic requirement with 0.3 µg/kg of dexmedetomidine compared to placebo.[18]

In our study, we noted a reduction in propofol dose needed for induction with a standard clinical sign (loss of verbal response and eyelash reflex) for titration of the drug dose.

CONCLUSION: Dexmedetomidine reduced the induction dose of propofol; a maximum reduction was seen along with 1 µg/kg followed by 0.6 µg/kg and 0.3 µg/kg. Hence, we conclude that 1 µg/kg and 0.6 µg/kg of dexmedetomidine offer a reduction in anaesthetic requirement.

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