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EFFECT OF IV DEXMEDETOMIDINE ON PERIOPERATIVE HAEMODYNAMICS STUDY AND REQUIREMENTS OF ISOFLURANE IN ELECTIVE SURGERY

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ABSTRACT

To study efficacy of Dexmedetomidine as adjuvant with general anaesthesia for following measure: Haemodynamic response during laryngoscopy ,intubation and intraoperative extubation & recovery and postoperative sedation and analgesia. After local ethical committee approval and written informed consent, a total of sixty patients (n=60) of ASA grade I or II aged between 18-55 years of either sex were randomly selected for this study. They were scheduled for elective surgeries of around two to three hours under general anaesthesia and divided in two groups (each group containing 30 patients).Pre-anaesthetic check-up was conducted and a detail history and complete physical examination recorded. After all investigations were done patients were explained about procedure and informed consent was taken. After applying all monitors and preloading patients with crystalloid 5ml/kg, both groups received premedication intravenous dose of 0.004mg/kg Glyccopyrolate,0.15 mg/kg Ondansetron, 1µg/kg Fentanyl before induction of anaesthesia. Before induction of anaesthesia, the group-D patients were given Dexmedetomidine 1µg/kg loading dose over 10 minute while group-S, patients received same volume of normal saline over 10 minutes All the patients in both the groups were monitored for VAS and sedation for at least 4 hours after surgery. Post-operative pain intensity was assessed using a 0 to 11 point VAS score. The loading dose of 1 µg/kg Dexmedetomidine, given over 10 min followed by continuous infusion of 0.6µg/kg/hr, as an adjuvant in general anaesthesia for elective surgeries provided a stable haemodynamic profile in perioperative period and effectively blunted pressor response to intubation and extubation, leading to minimal requirements for additional analgesics and potent inhalational agents

Key words: Dexmedetomidine, Inhalational agents, Cerebrovascular.

INTRODUCTION

In general anaesthesia laryngoscopy, intubation and extubation are noxious stimuli and associated with stress responses and haemodynamic change: hypertension, tachycardia and arrhythmias are well tolerated in otherwise healthy individuals but in patients with hypertension, coronary heart disease, cerebrovascular disease etc these transient changes can result in potentially deleterious effects To prevent and counteract these effects an ideal agent required which should be safe, titrable, and rapidly acting has both sedative and analgesic properties with less side effects [1].

A wide varieties of pharmacological agents like high dose of Opioids, Propofol, Xylocard

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, vasodilator drugs like Nitroglycerine, clonidine, were used to alternate these haemodynamic responses, alpha 2 adreno-receptor agents may provide an alternative to currently used adjuvant anaesthetic agents because of their anaesthetic sparing and haemodynamic stability. Clonidine is the prototype of alpha adrenoreceptor agonists and its preoperative administration has been shown to reduce intra operative haemodynamic changes. However its long half-life under anaesthetic condition has limited the use of clonidine [2-4].

With all these properties like sedative, anxiolytic, analgesic, sympatholytic with Dexmedetomidine is pharmacologically active D-isomer of Medetomidine has high selectivity for alpha 2 adrenergic receptor. Alpha 2 receptors are also located within CNS and their activation leads to sedation and reduction of tonic level of sympathetic outflow and augmentation of cardio vagal activity. This can result in a decrease heart rate and cardiac output. In addition alpha-2 receptors with in spinal cord modulate the pain haemodynamic stability and minimal respiratory depression render it suitable for sedation and adjuvant to anaesthetic agents during the whole perioperative period. The study was planned to compare the effects of Dexmedetomidine and normal saline on attenuation of haemodynamic changes and there effects as adjuvant in anaesthesia during elective surgeries [5-9].

MATERIALS AND METHODS

After local ethical committee approval and written informed consent, a total of sixty patients (n=60) of ASA grade I or II aged between 18-55 years of either sex were randomly selected for this study. They were scheduled for elective surgeries of around two to three hours under general anaesthesia and divided in two groups (each group containing 30 patients).

Exclusional Criteria

Patients posted for emergency surgical procedures ,patients with cardiovascular or respiratory ,renal disorders ,diabetes, hypertension ,obesity, difficult airways, pregnant ,currently breast feeding women, history of sleep apnea, psychiatric disorder were excluded from the study [10].

Preoperative Assessment

Pre-anaesthetic checkup was conducted and a detail history and complete physical examination recorded .Routine investigations like complete haemogram, random blood sugar, LFT, serum creatinine, chest x-ray(PA view), electrocardiogram were done.

All patients were explained about procedure and informed consent taken .All patients were explained about VAS. On the day of surgery, after shifting the patient to the operating room, patients base line values of heart rate, noninvasive blood pressure, pulse oximetry, electrocardiography were recorded [11].

An 18-gauge intravenous cannula was inserted and patients were pre-loaded with 5ml/kg of crystalloids. Both the group patients received premedication, intravenous dose of 0.004mg/kg Glyccopyrolate,0.15 mg/kg Ondansetron, 1µg/kg Fentanyl before induction of anaesthesia Before induction of anaesthesia, the group-D patients were given Dexmedetomidine 1µg/kg loading dose over 10 minute while group-S, patients received same volume of normal saline over 10 minutes .Heart rate ,mean blood pressure were recorded at the start of bolus drug injection ,at the end of bolus dose, and thereafter during intubation.

Induction

Balanced general anaesthesia was administered for all the patients. Induction was achieved with 5mg/kg intravenous thiopentone sodium. Intubation was facilitated after giving lignocaine 1mg/kg by 2mg/kg intravenous succinylcholine.

Maintenance

The lungs were ventilated by maintaining a tidal volume of 7-10 ml/kg .a frequency of 12 beats/minute, 3L/minute of fresh gas flow with 66% nitrous oxide with oxygen in closed circuit. Muscle relaxation maintain with 0.8 mg/kg of vecuronium intermittent bolus. Isoflurane inhalation was stared with0.6% in both the group's .Inj Dexmedetomidine maintenance infusion of 0.6µg/kg/hr started in group-D and saline infusion in group-S in the same dose. Routine monitoring consisted of HR, NIBP, SpO_2, ECG and ETISO, EtCO2 were recorded .The aim was to maintain HR and MAP within 20% of baseline values .the measurement were taken on the same arm throughout the study at the following times; base line ,after loading dose ,after intubation 5minutes,10minutes ,30minutes,60minutes,90minutes and 120 minutes, after infusion stopped, after reversal and extubation [12].

Intra operative bradycardia (pulse rate<50/min) was treated with inj Atropine 0.6 mg intravenously. Intra operative hypotension was treated with intravenous crystalloids and by reducing the Isoflurane concentration and inj mephentermine. An increase in HR and/or MAP >20% from base line values was treated by increasing the Isoflurane

concentration 0.2% increment as required .If there is no response within 5 minutes,1µg/kg Fentanyl was administered. Isoflurane inhalation and inj Dexmedetomidine was stopped at the time of skin closure. [13].

Reversal

On completion of surgery, the neuromuscular was reversed with 0.05mg/kg intravenous neostigmine and 0.008 mg/kg Glycopyrolate intravenously given.

Recovery Parameter

The extubation time was recorded together with the time to respond to simple verbal commands and the time for orientation.

Postoperative

All the patients in both the groups were monitored for VAS and sedation for at least 4 hours after surgery. Post-operative pain intensity was assessed using a 0 to 11 point VAS score on which 0 indicated no pain and 10 indicated the worst pain. Post-operative sedation was assessed at regular intervals postoperatively using Ramsay Sedation Scale.

Score	Response
1	Anxious or agitated or restless or both
2	Cooperative, oriented and tranquil
3	Drowsy but responding to commands
4	Asleep ,Brisk response to light glabellar tap or loud auditory stimulus

RESULTS

Table 1. Pulse Rate (beats/min)

Pulse Rate (beats/min)					
Time	**Group D**		**Group S**		**P Value**
	Mean	**SD**	**Mean**	**SD**	
Base line	83.40	9.4	79.87	9.33	>0.05
After Loading Dose	74.43	9.1	78.43	8.97	<0.05
Intubation	77.17	8.8	103.5	9.05	<0.05
5 Min after intubation	73.33	8.3	92.3	8.85	<0.05
15 Min after intubation	71.17	7.9	86.3	8.6	<0.05
30 Min after intubation	68.37	8.2	84.43	8.95	<0.05
45 Min after intubation	65.37	8.3	88.43	9.0	<0.05
60 Min after intubation	65.95	9.6	101.4	10.82	<0.05
90 Min after intubation	65.23	7.4	82.43	8.97	<0.05
120Min after intubation	71.83	8.5	88.33	6.12	<0.05
After infusion stopped	69.87	4.3	92.27	10.03	<0.05
Post extubation	68.33	3.1	86.33	8.03	<0.05

Table 2. Mean arterial blood pressure (mmHg)

Mean Arterial Blood Pressure (mmHg)					
Time	**Group D**		**Group S**		**P Value**
	Mean	**SD**	**Mean**	**SD**	
Base Line	96.01	6.1	94.8	6.82	>0.05
After loading dose	81.82	5.4	93.7	6.44	<0.05
INTUBATION	82.43	5.1	104.8	6.82	<0.05
5 Min after intubation	79.0	4.6	98.44	7.15	<0.05
15 Min after intubation	78.40	4.5	97.79	6.44	<0.05
30 Min after intubation	70.26	4.2	91.8	6.82	<0.05
45 Min after intubation	66.4	4.6	93.8	6.82	<0.05
60 Min after intubation	68.5	6.2	110.2	8.18	<0.05
90 Min after intubation	66.39	2.4	99.14	7.37	<0.05
120Min after intubation	77.5	3.1	99.08	7.99	<0.05
Infusion stopped	79.5	3.8	95.8	6.82	<0.05
REVERSAL	84.5	7.1	106.54	8.24	<0.05
Post extubation	86.77	3.8	100.29	7.45	<0.05

Table 4. End Tidal Isoflurane Concentration

Time	End Tidal Isoflurane Concentration					
	Group D		Group S		% Difference	P Value
	Mean	SD	Mean	SD		
5 min	0.51	0.14	0.66	0. 2	29.41	<0.05
10 min	0.55	0.13	0.67	0.15	21.81	<0.05
30 min	0.35	0.12	0.47	0.15	34.28	<0.05
45 min	0.35	0.13	0.61	0.15	42.62	<0.05
60 min	0.36	0.15	0.44	0.11	22.22	<0.05
90 min	0.33	0.09	0.44	0.11	33.33	<0.05
120min.	0.36	0.1	0.5	0.17	38.88	<0.05

Table 5. Recovery parameter

Time	Group D		Group S		P Value
	MEAN	SD	Mean	SD	
Extubation time(min)	5.16	1.08	5.1	1.06	>0.05
Respond to verbal command	6.17	1.18	6.8	1.06	>0.05
Time for orientation	8.53	1.04	7.6	0.8	>0.05

Table 6. Sedation Score

Time	Sedation Time				
	Group D		Group S		P Value
	Mean	SD	Mean	SD	
1 Hour	2.37	0.49	2.26	0.44	> 0.05 NS
2 Hour	2.4	0.56	2.53	0.50	> 0.05 NS
3 Hour	1.33	0.46	1.3	0.46	> 0.05 NS
4 Hour	1.00	0.0	1.0	0.0	> 0.05 NS

Table 8. Comparison Of Complication

Complication	Group D		Group S	
	No of PTS	%	No of PTS	%
Hypotension	2	9	0	
Hypertension	0		5	16
Bradycardia	3	10	0	
Tachycardia	0		6	20
Desaturation	0		0	

Fig 1

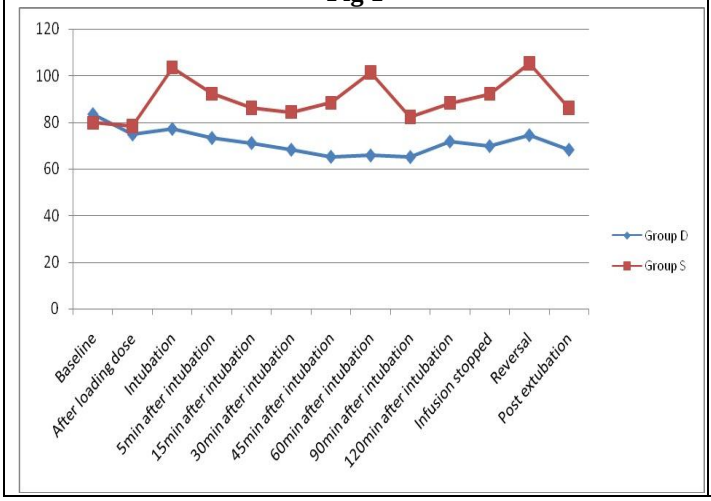


Fig 2

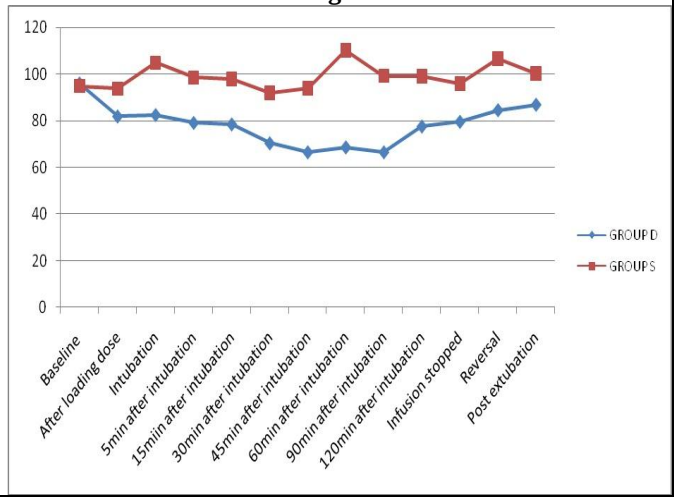


Fig 3

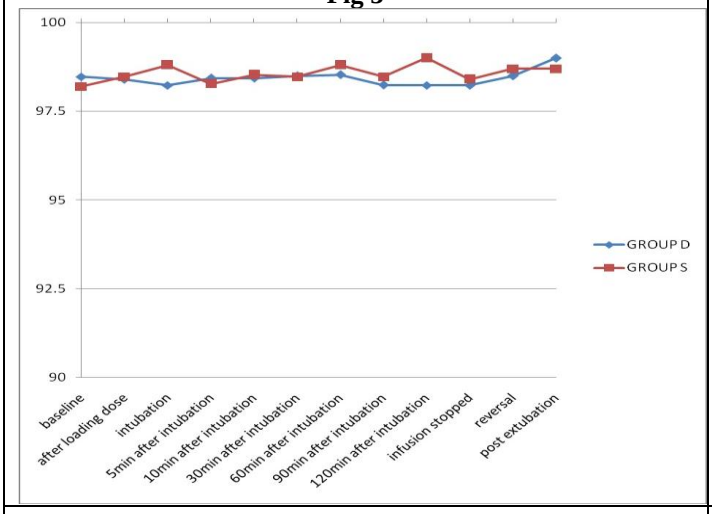


Fig 4. End Tidal Isoflurane Concentration

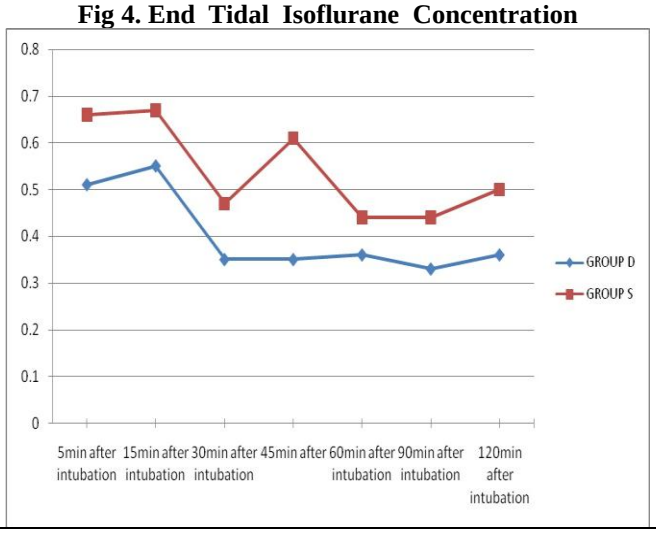


Fig 6. Sedation score

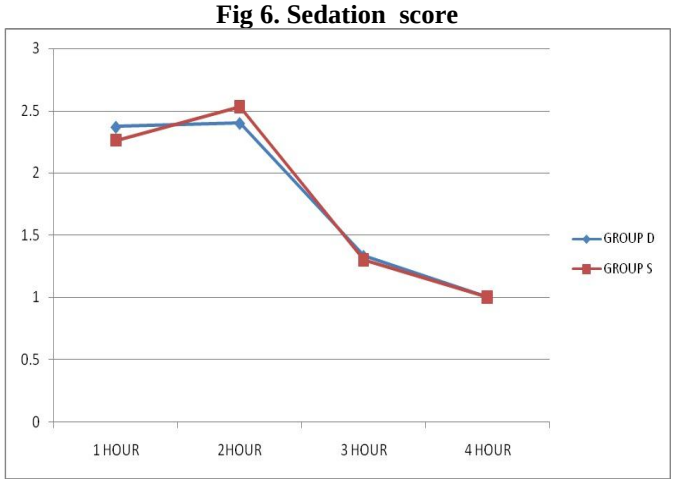
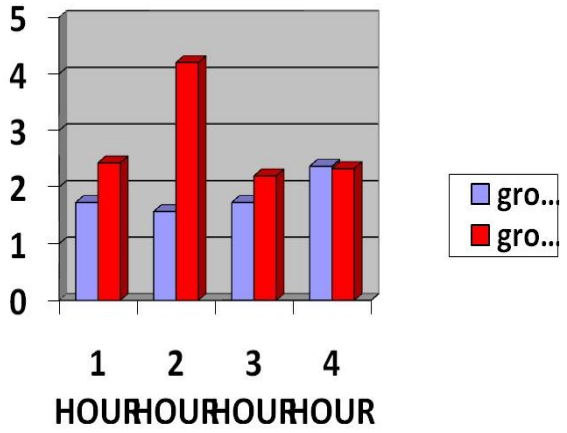


Fig 7



DISCUSSION

Hence a drug which can blunt both the heart rate and blood pressure response to laryngoscopy and intubation and intra operative surgical stress without having much adverse effect was required for this purpose. Dexmedetomidine is alpha-2 adrenoreceptor agonist which is pharmacologically active D-isomer of medetomidine .

The centrally acting alpha-2 adrenoreceptor agonist including Dexmedetonidine activate receptor in the medullary vasomotor center, reducing non-epinephrine turn over and decrease central sympathetic out flow, resulting in alteration in sympathetic function. There by suppressing the haemodynamic response to intubation, extubation without any side effect. Additional effects results from the central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus cereleus in the brainstem. The activation of alpha-2 adrenergic receptor in the dorsal horn of the spinal cord inhibits the release of sub-p, anociceptive mediator, resulting in primary analgesic effect as well as potentially of opoid induced analgesia [14].

In our study we found that bolus and intra-operative Dexmedetomidine infusion decreased haemodynamic response of various noxious stimuli and emergence from anaesthesia. Its haemodynamic effect are due to central sympatholytic action and cause a dose dependent reduction in a arterial BP and heart rate associated with decrease in serum nor epinephrine concentration.

In our study At intubation there was 3.68% rise in pulse from the base line in Group D as compared to 24.22% in Group S as shown in table-3. Intra-operatively, at 15 min post intubation pulse rate and mean blood pressure are significantly lower in Group D in comparison to Group S. The same trend was observed throughout intraoperative period as

shown in table-2 & 3. During extubation pulse rate value are increased by 6.21% in Group D & 12.43% rise in Group S as shown in table -3 and mean BP

rise 5.91% and 10.08% rise in respective group as shown in table-4.

Similarly, Bloor BC, Ward DS have observed a biphasic effect on hemodynamic after intravenous Dexmedetomidine in humans, an immediate increase in blood pressure (mediated by stimulation of peripheral stimulation of peripheral α-2 adrenoreceptors) followed by a longer lasting reduction in pressure caused by stimulation of α-2 adrenoceptors in central nervous system. Initial pressure effect is influenced by rate of intravenous infusion. They have observed this effect after giving 4µg/kg over 2 min period.

Lawrence did not observed such effect by infusing Dexmedetomidine over 5 min. similarly. In our study we have not observed this effect probably we have smaller dose (1µg/kg) given slowly over a period of 10 min

Lehtinen [7] where they found after administrating bolus dose of Dexmedetomidine there was decrease in heart rate after 10 min, post intubation increase blood pressure and heart rate was significantly less in Dexmedetomidine (0.6µg/kg/ hr) group than in the saline group. They found that, the post-intubation increase in heart rate was significantly less.

Jaakola showed that Dexmedetomidine attenuated the increase in HR and MAP during intubation.

Rao SH observed that loading dose of Dexmedetomidine 1 µg/kg, followed by a continuous infusion of0.5µg/kg/hour provided a stable haemodynamic profile in the perioperative period and a blunted presser response to intubation and extubation. With its use, there was a minimal requirement for analgesics and inhalational agents. It had an acceptable recovery profile.

Varshali M had observed Dexmedetomidine infusion in a dose of 1 µg/kg was given over 10 min before the induction of anaesthesia and was continued in a dose of 0.2-0.7 µg/kg/Hour until skin closure attenuated sympathoadrenal response to tracheal intubation and reduction in intraoperative anaesthetic requirement.

Yildiz of Dexmedetomidine 1 µg/kg blunted the hemodynamic responses during laryngoscopy, and reduced Opioid and anaesthetic requirements.

OXYGEN SATURATION

Oxygen saturation remained above 95 throughout the monitored period and there was no difference between groups.

END TIDAL ISOFLURANE REQUIREMENTS

The ability of α-2-adrenergic agonists to decrease anesthetic requirements has been previously described to their effect on central sympathetic transmission, since decrease in noradrenergic neurotransmission has been associated with a lowering of the MAC values. However some studies with Dexmedetomidine have suggested that other postsynaptic α-2 mechanism may also be involved. Sedation and analgesia probably account for the MAC-sparing effects of this class compound. Central α-2 adrenoceptors in the locus ceruleus and presumably by activating,nervous system and on to inhibition of release of receptors in the dorsal horn of' the spinal cord are likely involved in these effects. MAC reduction from Dexmedetomidine is much greater than with clonidine, presumably because of greater specificity of Dexmedetomedine for α2 adrenoceptors.

Lawrence CJ found out that single pre-induction intravenous dose of Dexmedetomidine 2µg/kg reduces the intra-operative Isoflurane requirements..

R Kanto [8] have documented decreased thiopental consumption'. was observed 47% Isoflurane MAC decrease after the association or intravenous Dexmedetomidine continuous infusion'. Khan found 35%-50% reduction in Isoflurane concentrations with either low or high doses of Dexmedetomidine

Aho [9] reported that a continuous intraoperative Dexmedetomidine infusion can decrease the requirement of Isoflurane up to 90% in healthy patients.

Similarly the endtidal Isoflurane concentration was significantly less in group-D as compared to group S($p<0.05$) in our study. As shown in table no-5 The overall mean end expiratory concentration of Isoflurane required during anesthetic maintenance was 31.79% less in Group D as compared to Group S. Maximum difference in Isoflurane requirement after intubation is 42.62% less in Group D as compared to Group S. This may be because attenuation of intubation response by Dexmedetomidine infusion so that less concentration of Isoflurane required to maintain the target haemodynamic level.

The pharmacodynamic effect of Dexmedetomidine may aid in reducing the concentration of anaesthetics used and preventing adverse effects such as hepatic and renal toxicity, severe myocardial depression, and the greenhouse effect.

INTRAOPERATIVE INCREAMENTAL DOSE OF ANALGESIC

Ozcan B [11] Intraoperative infusion of Dexmedetomdine reduces perioperative analgesic requirements.

We found that Dexmedetomidine provide analgesia and reduce dose requirement. The requirement of Fentanyl was reduced in the Dexmedetomidine group in our study.

Recovery time parameter

Akshu [9] suggest that Dexmedetomidine 0.5 µg/kg intravenously administered before extubation, was more effective in attenuating airway reflex responses to tracheal extubation and maintaining haemodynamic stability without prolonging recovery compared with Fentanyl 1µg/kg intravenously in these patients undergoing rhinoplasty. Turan [13] found that Dexmedetomidine improved extubation conditions but did not prolong recovery in patients presenting for craniotomy.

In our study we observed comparable recovery parameter like extubation time, response to verbal command, and time for orientation in both groups. Time to eye opening on verbal commands was similar in both the groups. After intravenously infusion, Dexmedetomidine has a rapid distribution phase, with a distribution half-life of approximately 120 minute which might be the explanation for early recovery.

POST OPERATIVE OBSERVATION

Sedation and VAS Score

Sushil Nayek where they found that Dexmedetomidine caused sedation but did not cause any delay in recovery time. In another study of Judith E. Hall, tons Uhrich et[25] all it was found that small dose Dexmedetomidine infusions caused sedation, impairment of memory and psychomotor per While they did find some amount of sedation by Dexmedetomidine in the course of our study, they did not find any memory loss or psychomotor impairment in any of their patients.Dexmedetomidine provides sedation and analgesia with no accompanying respiratory depression. In our study, VAS for pain score was less in group D relative to group-S.

Post-operative complications

C.J. Lawrence [13] reported higher incidence of hypotension and bradycardia following intramuscular Dexmedetomidine. This may be because of higher intramuscular dose of Dexmedetomidine in their study.

Thus Dexmedetomidine infusion of 0.6µg/kg/min is not associated with significant complication and side effect in our study. No allergic phenomena were observed. During intraoperative period Atropine was required to treat bradycardia in 3 patients in Dexmedetomidine group and 2 patients develop hypotension in group S and corrected with intravenous fluid administration'

Limitations of study

Because of lack of good clinical indices to determine the anaesthetic depth, haemodynamic end points were employed. It may be argued that these are not optimal for assessing depth, particularly when hemodynamic active drug is being studied and patients may actually have received unusually light anesthesia; however, this argument is not supported by the clinical observations in our study, since none of our patients complained of intraoperative awareness. Nevertheless, the possibility that the diminished Isoflurane requirements may have been partly the result of bradycardic effect of Dexmedetomidine cannot be totally excluded.

Another limitation in our study is we that have not measured plasma concentration of catecholamines as stress marker of sympathetic response to intubation and extubation.

CONCLUSION

The loading dose of 1 µg/kg Dexmedetomidine, given over 10 min followed by continuous infusion of 0.6µg/kg/hr, as an adjuvant in general anaesthesia for elective surgeries provided a stable haemodynamic profile in perioperative period and effectively blunted pressor response to intubation and extubation, leading to minimal requirements for additional analgesics and potent inhalational agents. There was also an acceptable recovery profile and postoperative undesirable adverse events were comparable and manageable.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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