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Research Article

A comparative study of haemodynamic responses to intubation: Dexmedetomidine 1µg/kg VS Clonidine 1 µg/kg

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Abstract

Objectives: To compare the effects of Dexmedetomidine (1µg/kg) and Clonidine (1µg/kg) on haemodynamic responses to endotracheal intubation, effect on anaesthetic requirements and effect on sedation.

Material and Methods: In this prospective double blind study, 60 patients scheduled for elective surgeries under general anaesthesia were randomly divided into two groups Group D (Inj. Dexmedetomidine dose 1µg/kg iv) and Group C (Inj. Clonidine dose 1µg/kg iv). Patients belonging to ASA I & ASA II of both sexes aged 20-60 years, were included in this comparative randomized study. Pulse, blood pressure, ECG were monitored continuously and recorded before giving the study drug, after giving the study drug, at intubation then at1,3,5,10 minutes after intubation. Data were analysed and $p<0.05$ was considered significant.

Result : Dexmedetomidine group had 4.70% rise in heart rate at time of intubation and Clonidine group had 9.59% rise which was statistically significant($p<0.05$), except during intubation,difference in heart rate between two groups was not significant.($p>0.05$))

Group C had significant rise in SBP and DBP during intubation compared to Group D.Maximum rise in SBP and DBP in Group C was 14.53% and 12.84% respectively, whereas in Group D it was 5.55% and 8.90% respectively.

Dexmedetomidine group had better sedation than Clonidine group. ($p<0.05$)

Conclusion: Dexmedetomidine significantly attenuated the sympathetic response of laryngoscopy and intubation as compared to Clonidine.

Keywords: Dexmedetomidine, Clonidine, hemodynamic changes and endotracheal intubation.

1. Introduction

In 1940, Reid and Brace first described hemodynamic response to laryngoscopy and intubation[1]. The circulatory perturbations stem from reflex sympathetic discharge due to epipharyngeal and laryngopharyngeal stimulation, and are marked by rise in circulating plasma adrenaline and noradrenaline concentrations with consequent increase in arterial blood pressure, heart rate and oxygen consumption.[2,3] The magnitude of the response is greater with increasing force and duration of laryngoscopy.[4]

The rise in pulse and blood pressure are usually transitory, variable and unpredictable. These changes are of no consequence and are well tolerated by healthy individuals. But these above mentioned effects may have serious repercussions on the high-risk patients like those with hypertension, heart disease and coronary artery disease.Therefore attenuation of such responses is of great importance in the prevention of the perioperative morbidity and the mortality.[5] Many non-pharmacological and pharmacological methods have been tried by various authors to attenuate the cardiovascular response to laryngoscopy[1,6,7,8,9,10], but no single anaesthetic technique has become generally accepted as being effective in preventing or attenuating these responses.[11]A basic need is continuously felt among the anaesthesiologist fraternity for desired availability of a drug that effectively suppresses all the hazardous responses to noxious stimuli with a maximum safety margin. Since sedation, anxiolytic and antisialagogue action are attractive attributes in a premedication agent prior to anaesthesia, administration of α 2 agonist suits this purpose well.[12]

Both Clonidine and Dexmedetomidine have actions on both alpha-1 and alpha-2receptors, but Dexmedetomidine is highly specific and selective alpha-2 adrenoceptor agonist with alpha-2: apha-1 binding selectivity ratio of 1620:1 compared to 220:1 for Clonidine.Dexmedetomidine (dextro isomer of medetomidine) was introduced in1999 and its advantage in anaesthesia setting include sedation, analgesia, anxiolysis & improved hemodynamic stability by the activation of alpha -2 receptor located in the post synaptic terminals in the central nervous system, which causes augmentation of vagal activity[13,14,15,16]. Clonidine (a centrally acting α_2 adrenergic agonist) has been investigated and prescribed first as an antihypertensive drug in the 1950s. Intravenous Clonidine has found new uses later, including treatment of some types of neuropathic pain, opioid detoxification, and sleep hyperhidrosis.

Through this study, we tried to compare the effects of Dexmedetomidine and Clonidine on hemodynamic responses to endotracheal intubation, effect on anaesthetic requirements and effect on sedation to help the selection of a better drug.

2. Material and Method

After ethical committee approval in this prospective double blind study 60 patients were randomlyallocated into two equal groups (n=30 each). These patients were included in the study only after obtaining a written informed consent.

Patients aged between 18 -60 years of ASA I & II posted for elective surgeries under general anaesthesia were included in this study. Patients with history of any cardiac, renal, hepatic & cerebral diseases were excluded from the study. Patients with predicted difficult airway, pregnant females, patients on beta blocker and patients with history of allergy to any drug were also excluded from this study.

2.1 Allocatioon of groups

Group D (D-Dexmedetomidine):(n=30) received 1µg/kg body weight of Dexmedetomidine intravenously.

Group C (C-Clonidine): (n=30) received 1µg/kg body weight of Clonidine intravenously.

A routine pre-anaesthetic checkup including medical history and systemic examination was carried out. Routine and special investigations were done accordingly. The patients were kept Nil per mouth for 6 hrs before surgery.

On arrival in operation theatre after starting iv fluid baseline parameters were recorded, which included, heart rate (HR), mean arterial blood pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), ECG and SpO_2. All patients were premedicated with Inj. Glycopyrrolate 0.2mg, Inj. Ondansetron 4mg iv. All patients were preoxygenated via face mask. Group D Patients were given intravenous Dexmedetomidine 1µg/kg body weight diluted in 10 ml normal saline using syringe infusion pump over 10 minutes.Group C patients were given intravenous Clonidine 1.0 µg/kg body weight diluted in 10 ml normal saline,using syringe infusion pump over 10 minutes.

The double blind design of the study was assured by the fact that an anesthesiologist not further involved in the study prepared syringes containing study drugs before induction of anaesthesia. The anaesthesiologist responsible for the anaesthetic technique is thus kept unaware of the contents of the syringes. The observing anaesthesiologists were also blinded for the study drug.

The entire patients received Inj Tramadol 1.5 mg/kg iv,before induction of anaesthesia After waiting for 3 min. patients were induced with 2.5% Thiopentone till the loss of eyelash reflex. The dose of Thiopentone required for induction was noted for both groups. Succinylcholine 2mg/kg body wt. was given for intubation. One minute after succinylcholine, patients were intubated with appropriate sized cuffed endotracheal tubes with gentle laryngoscopy done within 15 seconds. We excluded the patient who had taken>15 sec. for intubation. Anaesthesia was maintained with oxygen and nitrous oxide (50%-50%), 1 % isoflurane and Inj. Vecuronium bromide- 0.08mg/kg body weight as initial dose and 1mg as and when required. After the surgical procedure, patients were reversed with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.04mg/kg iv.

Hypotension (reduction in arterial pressure of 30% or more from the baseline was treated primarily by increasing the iv infusion rate, and then with10 mg bolus dose of ephedrine. Bradycardia (heart rate less than 45 beats /min) was treated with 0.6 mg of atropine.

After extubation all the patients were monitored in the post operative recovery room for 24 hours. All the patients were observed for any complication like nausea, vomiting, sedation, respiratory depression bradycardia and hypotension.

2.2Parameters Studied

A.Hemodynamic responses were compared in both groups by measuring

Heart rate (HR) ,Systolic blood pressure (SAP),Diastolic blood pressure(DAP),Mean arterial pressure (MAP).These parameters were measured using automatic multiparameter monitor- STAR PLUS-LARSEN & TOUBRO INDIA LIMITED, at following intervals.

1. Before giving the test drug (Base line values)
2. 3 min. after the end of infusion of study drug.
3. During induction of anaesthesia.
4. During intubation
5. After intubation at 1 min, 5 min, 10 min.

B.Sedation scoring was done as per RAMSAY sedation scale 3min. after completion of study drug infusion.

C.**Total dose of thiopentone used for induction was recorded.**

2.3 Statistical Method Employed

Statistical analysis was done with non-paired (two tailed, independent) student t-test for continuous data and discrete data was validated and analysed using Graph pad prism.

Microsoft word and excel was used to generate tables.

Results were expressed as mean ± SD.

P-values:p>0.05- Statistically not significant (NS); p<0.05- Statistically significant (S); p<0.01- Statistically highly significant (HS); p<0.001- Very highly significant.

The observation data were gathered from proforma, and they were expressed in the form of charts and tables.

3. Result

Both groups were comparable in their age, gender and body weight distribution.ASA grading was also similar (p>0.05).After administration of drug HR decreased in both groups but the difference was statistically insignificant (p>0.05).Both groups had rise in HR at intubation that was 4.7% in group D and 9.59% in group C and difference was statistically significant (p<0.05). But at 1,3,5 and 10 min after intubation difference in HR between two groups was not significant.

Similar to HR, SBP &DBP also decreased after dexmedetomidine and clonidine administration but fall in BP was more in group D compare to group C (p<0.05).Both group had maximum rise in SBP at intubation that was 14.53% in group C and 5.55% in group D which was statistically highly significant (p<0.0001).

Difference in SBP between two groups remained statistically highly significant at 1,3,5 and 10 min after intubation. It achieved 9.12 % lower than the basal value in group D at 10 min post-intubation compare to only 0.081% lower than basal SBP in group C.

Similarly both group had maximum rise in DBP at intubation that was 8.90% with dexmedetomidine whereas 12.84% with clonidine which was statistically significant (p<0.05).This significant difference in DBP between two groups last till 10 min after intubation and in group D DBP at 10 min after intubation was lower than basal value whereas in group C it was above baseline DBP.Average sedation score in group D was higher compare to group C and it was statistically significant (p <0.05) but average thiopentone requirement for induction between two groups was comparable(p>0.05).

4. Discussion

The hemodynamic response to laryngoscopy has been a topic of discussion since 1940. These responses can be detrimental in elderly and haemodynamically compromised patients due to increase in arterial pressure, heart rate and oxygen consumption. Therefore controlling this perioperative stress response is an important goal of modern anaesthesia.[18,19,20]

Many pharmacological methods were evaluated either in premedication or during induction to attenuate these adverse hemodynamic responses but the drugs which were used where either partially effective or they produced other undesirable effects.[11]

Various Studies are done with different doses of Dexmedetomidine and Clonidine[17,21,22,23].Sagirogluet *al*[24] conducted study with different doses of dexmedetomidine to control hemodynamic responses to intubation and he found that dexmedetomidine 1 µg /kg is more effective than 0.5 µg/kg without any side effects. The effects of clonidine on the hemodynamic variables are dose related but this dose of Clonidine (1 µg /kg) was consider appropriate to provide adequate clinical effects.[22]

Table 1: Demographic Characteristics

	Group D	Group C	P-value
Age (years)	39.77 ± 2.307	34.27 ± 2.029	0.0786
Sex (M/F)	13/17	17/13	
Weight(kg)	53.27 ± 1.407	55.40 ± 1.659	0.3308
ASA (I/II)	16/14	18/12	

Similar to our study Bijoy Kumar *et al*[17]& Shirsendu *et al*[23]who have done comparison of clonidine and Dexmedetomidine and have also found fall in HR after its infusion.Scheinin *et al*[25] reported that use of α2 agonist leads to bradycardia.

During intubation there was rise in heart rate in both the groups which was more in group C compare to group D and this rise in HR in group C was statistically significant (p< 0.05) (table no-2) Similar to our result Shrisenduet *al*[23]has also found statistically significant rise in HR during intubation in

clonidine group compare to dexmedetomidine. In his study this statistically significant higher HR in clonidine group last upto 3 min after intubation but in our study, 1 min after intubation there was no statistically significant difference in HR between two groups (p > 0.05).Bijoy Kumar *et al*[17] in his study found rise in HR after intubation with only clonidine but not with Dexmedetomidine.

Table 2: Comparison of changes in mean Heart Rate (HR) between Group D & Group C

Time	Group- D		Group- C		P- Value
	Mean ±SD	**% Change from baseline**	**Mean ± SD**	**%Change from baseline**	
Basal	86.27±1.447	-	86.23±2.027	-	**0.989**
After study drug	77.00±0.8037	**↓10.74**	76.93±0.824	**↓10.78**	**0.9540**
At induction	75.60±1.429	**↓12.36**	77.83±1.714	**↓9.74**	**0.3211**
After intubation	90.33±1.431	**↑4.70**	94.50±0.5023	**↑9.59**	**0.0080**
1 min after intubation	86.13±1.276	**↓0.16**	88.50±1.593	**↑2.63**	**0.2509**
3 min. after intubation	84.20±1.517	**↓2.39**	84.30±1.795	**↓2.23**	**0.9662**
5min after intubation	81.73±1.462	**↓5.26**	81.63±1.814	**↓5.33**	**0.965**
10 min after intubation	79.10±1.892	**↓9.06**	80.40±1.650	**↓6.76**	**0.6065**

A biphasic cardiovascular response has been described after the administration of Dexmedetomidine[26]. A bolus of 1µg/kg results in a transient increase in arterial blood pressure and reflex decrease in heart rate is due to α2 receptor stimulation of vascular smooth muscle. This can be markedly decreased by slow infusion over 10 min. In our study this effect was not noticed due to the slow infusion of the drug over 10 min.[27]

Similarlyto our studyCelik *et al*[24] and Nermin *et al*[28] found fall in BP after infusion of Dexmedetomidine andGupta *et al*[22] found fall in BP with Clonidine .

Earlier studies have demonstrated transient increase in HR and MAP initially within 3to 5 min of dexmedetomidine infusion, which is followed by a decrease[29,30] and is probably due to the vasoconstriction effect of dexmedetomidine appearing earlier than the central sympathetic action. However we have not noticed this transient rise in HR and BP.

During intubation both groups had maximum rise in SBP but this was more in Group C than in Group D. There was 6% rise in SBP in Group D from baseline SBP whereas Group C had 15% rise, which was statistically highly significant (p<0.001) (Table-3). Similar to our study Shirsendu *et al*[23] has also noticed significant rise in SBP in clonidine group almost 14.67% than in Dexmedetomidine where rise in SBP was only 7%. Bijoy Kumar *et al*[17] has also found comparatively more increase in SBP with Clonidine than Dexmedetomidine.

Table 3: Comparison of changes in mean systolic blood pressure (SBP) between Group D & Group C (in mmHg)

Time	Group- D		Group- C		P- Value
	Mean ±SD	**% Change from baseline**	**Mean ± SD**	**%Change from baseline**	
Basal	126.1 ± 1.281	-	122.5 ±1.189	-	0.0439
After study drug	113.1 ±2.188	↓10.3	115.9 ±1.490	↓5.38	0.0.029
At induction	110.3 ±1.839	↓12.7	114.7 ±1.099	↓6.19	0.0445
At intubation	133.1 ±0.9132	↑5.55	140.3 ±1.283	↑14.53	<0.001
1 min after intubation	127.5 ±1.531	↑1.11	134.3 ±1.071	↑9.63	0.006
3 min. after intubation	126.5 ±1.844	↑0.31	128.1 ±0.9916	↑4.57	0.0012
5min after intubation	119.7 ±1.908	↓5.07	125.3 ±0.8156	↑2.28	0.0091
10 min after intubation	114.6 ±1.797	↓9.12	122.4 ±1.288	↓0.081	0.0008

Similar to SBP, DBP had significant rise in Group C in response to intubation compare to Group D (p< 0.05). (Table-4)

Table 4: Comparison of changes in mean diastolic blood pressure (DBP) between Group D & Group C (mmHg)

	Group- D		Group- C		P- Value
Time	**Mean ±SD**	**% Change from baseline**	**Mean ± SD**	**% Change from baseline**	
Basal	80.87±1.679	-	81.53±1.049	-	0.7376
After study drug	76.67±1.082	↓5.19	80.60±0.8032	↓1.14	0.0050
At induction	76.07±1.437	↓5.93	80.53±1.015	↓1.22	0.0138
At intubation	88.07±1.270	↑8.90	92.00±0.9965	↑12.84	0.0179
1 min after intubation	84.87±1.379	↑4.94	91.20±1.306	↑11.86	0.0015
3 min. after intubation	80.93±1.253	↑0.07	89.60±1.160	↑11.86	<0.0001
5min after intubation	78.33±1.131	↓3.14	85.53±1.129	↑4.90	<0.0001
10 min after intubation	76.53±1.02	↓5.36	83.13±1.137	↑1.96	<0.0001

During laryngoscopy and intubation and immediately after it, rise in the HR and Blood pressure was maximum, these findings are in agreement with the studies done by Smith and Derbyshire[31] and Shribman *et al*[18],who concluded that the plasma catecholamine concentration increased to the maximum within 1 min after intubation.

In both groups SBP & DBP started falling immediately after intubation but rate of fall in BP was more gradual in group C, so Dexmedetomidine was more efficient in the attenuation of rise in MAP compared to Clonidine in response to intubation.

Similarly, Scheinin *et al*[25]has proved that Dexmedetomidine attenuate the cardiovascular response to laryngoscopy and intubation by measuring catecholamine concentration and found that the concentration of noradrenaline in mixed venous plasma was smaller in the Dexmedetomidine group during all phases of induction.

Table –5 shows average dose of thiopentone use for induction in both groups which is little higher in group C compare to Group D but it was statistically insignificant (p> 0.05). Shirsendu*etal*[23] has noted mean induction dose of Propofol was significantly less in Dexmedetomidine than Clonidine group. Aantaa and co-workers have demonstrated the anaesthesia potentiating effects of clonidine and dexmedetomidine.[32,33]

Ramsay sedation score in group D was higher than group C (p < 0.05) (Table no 5). Shirsendu *et al*[23] has also showed statistically higher Ramsay sedation score with Dexmedetomidine than with Clonidine. The major sedative and antinociceptive effects of Dexmedetomidine are attributable to its stimulation of α2 A subtype located in locus ceruleus.[34]It is the 8 times more specificity of Dexmedetomidine for α2 receptor that makes it a more effective sedative and analgesic agent than Clonidine.[34]

Table 5: Comparison of Average Dose of Thiopentone and Average Ramsay Sedation Score between Group-D and Group-C

	Group- D	**Group- C**	**p-value**
Average dose of thiopentone (mg)	425±5.51	475±8.08	0.365
Average Ramsay Sedation Score	2.65±0.35	1.95±0.51	<0.05

Even though higher sedation score seen with Dexmedetomidine was not associated with fall in SpO_2. Similarly Shirsendu *et al*[23] and Sagiroglu *et al*[24]also found no respiratory depression or decrease in SpO_2 with similar doses of Dexmedetomidine, so we can conclude that Dexmedetomidine doesn't cause significant respiratory depression .

The present study finding corroborate with those of previous studies. No adverse effects from the drug were seen in the present study. However, the effect was seen in ASA I/II patients, but the usefulness will be of immense help in high risk patients.

5. Conclusion

Based on the present clinical comparative study, the following conclusion can be made:

- Dexmedetomidine significantly attenuated the sympathetic response of laryngoscopy and intubation. Thus this study showed that Dexmedetomidine is superior to Clonidine in the attenuation of the pressure response of laryngoscopy.
- Dexmedetomidine is helpful providing sedation and also decreases the dose of requirement of anaesthetic agent for induction.

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